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Charles Virgil Mosby
1876—1942

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In Memoriam

CHARLES VIRGIL MOSBY

1876-1942

WITH the death of Dr. Mosby on November 9, 1942, an outstanding and interesting personality has passed out of the American medical publications field. From small beginnings and in the face of many trials, he built up one of the largest organizations of its kind in this country.

It is not generally known that Dr. Mosby was a physician. He graduated from the St. Louis College of Physicians and Surgeons in 1900. He practiced for a while but gave it up for a career in medical publishing because he felt this offered greater opportunities for service. It became his life work and his success in this chosen field was based on his determination, foresight, and a dynamic personality. To accomplish his purposes, he traveled back and forth over this country extensively, he became personally acquainted with the medical men whose books he published, he attended numerous society meetings, he never spared himself, and he inspired his large business staff with his own ambitions and devotion to the organization which he had established.

When the predecessor of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY was compelled to terminate its long career because of the situation developed by the previous World War, the undersigned encountered a great deal of difficulty in finding another publisher, due to the resultant financial depression and a hesitancy to undertake new projects. Through mutual friends, Dr. Mosby became interested in the venture. He agreed to publish the present journal without subsidies and with its editorial policy under the complete control of the medical profession. During the many years of my association with him, he has never interfered with this policy and, in the face of many difficulties, built up the circulation of the JOURNAL to its present large proportions. For this the profession owes him a debt of gratitude and appreciation.

GEORGE W. KOSMAK, M.D.

Original Communications

APPLICATION OF THE NEW CLASSIFICATION OF TOXEMIAS OF PREGNANCY IN 318 FATAL CASES*

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DURING recent years there has been a steady and continued improvement in maternal welfare as evidenced by the statistical index, namely, the maternal mortality rate. The group of infections comprising puerperal sepsis always has been the individual high cause of maternal mortality, with toxemia of pregnancy a close second. In the United States in 1940 puerperal sepsis was responsible for 41 per cent of the puerperal deaths and toxemia of pregnancy for 25 per cent. In the five years just past, the reduction in the rate of maternal deaths in the United States from the toxemias (24 per cent) has lagged behind the reduction in infection deaths (31 per cent). However, in 13 Southern states, toxemia led from 1936 on through 1939 as the cause for the highest proportion of maternal deaths.

Obstetricians, until quite recently, have been primarily interested in the toxemia problem from the standpoint of immediate mortality to mother and child. Largely due to the efforts of Herriek and Tillman¹⁻⁴ attention was called to the equally important remote effects of toxemia on the vascular system of the mother. Internal medicine, at long last, has become interested in the toxemias of pregnancy from this standpoint as well as from the standpoint of their importance in regard to the whole problem of the etiology and pathogenesis of hypertensive-vascular disease. In reality, toxemia of pregnancy represents an acute experiment in hypertension; it awaits only clinical and laboratory investigations which will aid in furnishing an answer to the most important disorder in occidental medicine, essential hypertension. It is a sad commentary on specialization in medicine that the realization of this important fact has been so long delayed.

The subject of renal vascular disease and pregnancy has been a confused one for several additional reasons. First, because of the old belief that the toxemia of pregnancy was of "nephritic" origin and that the convulsive seizures were "uremic." Second, because of the failure to differentiate glomerulonephritis, pyelonephritis, and essen-

*Read at a meeting of the Philadelphia Obstetrical Society, May 7, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

tial hypertension complicated by pregnancy. Third, the attempt to remedy this situation by the invention of such unsatisfactory terms as substandard or low reserve kidney.

The relation of the toxemia of pregnancy to the kidney is very much like the arteriosclerotic-hypertensive problem to which, indeed, it is closely related. When we first became aware of the importance of high blood pressure from a clinical standpoint, it was thought that arteriosclerosis was responsible and that the patient was doomed to die of kidney disease. About the turn of the present century, largely due to the efforts of Allbutt in England, Huchard in France and Janeway in America, we learned that most hypertension was of nonrenal origin, that is, it was of the so-called "essential" variety, and instead of being caused by arteriosclerosis, the situation was just the reverse, it was a vasospastic disorder which resulted in thickening and stiffening of the blood vessels and hence, was responsible for arteriosclerosis. However, it took us about twenty-five years to absorb this new teaching, and just when we felt that we had emancipated ourselves from the idea that the kidneys were responsible for hypertension, Goldblatt, by his very ingenious experiments on dogs, led us right back to the renal origin of hypertension.

Now the situation in regard to kidney disease and the toxemia of pregnancy has run a similar circular course. Originally, it was held that toxemia was nephritic in origin and then gradually we came to the opposite conclusion, that the toxemia of pregnancy was not of renal origin but instead that it arose from some unknown "toxic" cause and resulted in damage to the vascular system and kidneys.

We are now prepared, therefore, to look upon toxemia of pregnancy (the vascular syndrome of pregnancy) as a remarkable opportunity for the study of the interrelated factors which may have to do with that much more common and more important disease to which toxemia is related, namely, essential hypertension.

Some years ago the American Committee on Maternal Welfare felt that more rapid progress in reducing the mortality from the toxemias could be accomplished if a standardized classification was available. This move, it was felt, might lead to more accurate knowledge of incidence of the various forms and the results of their treatment.

Progress in an understanding of heart disease was greatly accelerated when a standardized classification and precise terminology led to more exact diagnosis. The same can be said for kidney disease, which, up to the time of the introduction of the now generally accepted classification of Volhard and Fahr in 1914, was a poorly understood and, consequently, poorly handled subject. Since that time progress has been rapid.

A definite advantage of the new classification of the toxemias of pregnancy is that it brings us a little closer to a better understanding of the renal and vascular syndromes that are often called toxemia of

TABLE I. CLASSIFICATION AND DISTRIBUTION OF 318 FATAL CASES

Group A. Disease not peculiar to pregnancy	
I. Hypertensive disease (hypertensive cardiovascular disease)	
a. Benign (essential), mild, severe	13
b. Malignant	3
II. Renal disease	
a. Chronic vascular nephritis or nephrosclerosis	10
b. Glomerulonephritis	
(1) Acute	3
(2) Chronic	10
c. Nephrosis	
(1) Acute	1
(2) Chronic	0
d. Other forms of severe renal disease	9
Group B. Disease dependent on or peculiar to pregnancy	
I. Pre-eclampsia	
a. Mild	
b. Severe	63
II. Eclampsia	
a. Convulsive	143
b. Nonconvulsive (that is, coma with findings at necropsy typical of eclampsia)	13
Group C. Vomiting of pregnancy	37
Group D. Unclassified toxemias	13

pregnancy. Just as the effort is now being made to classify the hypertensive disorders and get away from the term "essential hypertension," so we must realize that many conditions that are called toxemia can be broken up into separate entities.

Shortly after its proposal the classification was adopted in a large number of clinics and, based upon the proposed grouping, attempts were made to review series of cases of toxemia establishing the final diagnosis by follow-up studies lasting over a variable period of time. Although results were not uniform as to the incidence of the various forms of toxemia in different clinics, and difficulties were often encountered in the proper assignment of cases, even after follow-up studies, the effort as a whole has met with general approval.

The authors having at their disposal from the files of the Committee on Maternal Welfare, Philadelphia County Medical Society, 1931-40, the histories of 1,790 maternal deaths which had been critically analyzed and reviewed, felt that it might be of value to separate the cases of toxemia of pregnancy and attempt to apply new classification to that group.

Inaccuracies and incompleteness of diagnosis on death certificates of the first three years already had been shown to be present in almost 10 per cent of the eclampsia group. Many other instances of toxemia were hidden under the diagnoses of sepsis, hemorrhage, and accidents of labor. A careful search of the 1,790 histories revealed 318 cases in which some type of toxemia of pregnancy had been present, and these were used for the discussion of the problem at hand.

The histories were thoroughly studied from various standpoints, such as antecedent medical and obstetric history, physical examination, time of onset and clinical course of the fatal illness, laboratory procedures, and autopsy findings. Although many items were lacking in one history or another sufficient evidence was present in the majority of cases to arrive at a conclusion as to the proper classification.

Group A. Disease Not Peculiar to Pregnancy

In Group A, disease not peculiar to pregnancy, there are grouped hypertensive and renal disease with various subheadings. Hypertensive disease (hypertensive cardiovascular disease) is classified as benign (essential), mild, and severe; and malignant.

A.I. Hypertensive Disease

Hypertensive Disease, Benign, A.I.a.

We decided that 13 cases fell in Group A.I.a. In this group the average age was approximately thirty-five years. All the women had been previously pregnant, with an average of 5 pregnancies for each woman. Nine, or practically 70 per cent of the group, had had previously abnormal pregnancies. Four of the women were markedly obese. Previous hypertension was mentioned as such in the histories of 5 women. Nephritis, apart from hypertension, was mentioned in 2 others, cardiac disease in 2; while there were additional factors having to do with the cardiovascular or renal systems, such as cerebral hemorrhage in 1, and pyelitis in 2 cases.

Symptoms appeared in the first trimester in 3 cases, in the second trimester in 1 case, and in the last trimester in 5 cases. Although not mentioned in the remaining 4, it was felt that the time of appearance of symptoms might not have been noted because of delay in seeking prenatal care.

A latent vascular disease in some instances of late appearance of symptoms may have been stimulated by the pregnancy, and only noted when the patient was first seen in the last trimester. If patients to be classified properly in this group do not appear early for prenatal care, there is no opportunity to discover symptoms or offer appropriate medical advice. It is to be regretted that in this group, indeed, in the whole group of toxemia cases, insufficient attention was paid to the ophthalmoscopic examination. Only two of this group had eye ground observations; both were confirmatory of hypertensive-vascular disease.

On the other hand, blood chemistry tests were routinely performed. As a matter of fact more observations on urea, and also uric acid, creatinine and nonprotein nitrogen were done than were actually necessary. Obviously more attention has been given to blood chemistry in the toxemias of pregnancy than to physical examinations or ophthalmoscopic studies. Perhaps they were easier to obtain. The place for the ophthalmoscope has now been solidly established in the study of the toxemia of pregnancy and at the same time less importance is attached to estimations of the nonprotein nitrogenous constituents of the blood.

From the standpoint of obstetrics, 6 hysterotomies, vaginal or abdominal, were performed, and 3 surgical inductions of labor, 1 followed by version and extraction, and 1 by forceps. Two women died

undelivered and only 1 fetus was born alive. Only 4 cases came to necropsy.

On the original death certificates there were found repeatedly ambiguous and inexact terms, such as chronic nephritis and uremia, chronic myocarditis, and acute cardiac dilatation. Due to a lack of precision on the certification of death, it would have been difficult to classify this group under the old terminology, and in this respect, the new classification is a distinct advance.

Hypertensive Disease, Malignant, A.I.b.

There were three histories for which this group seemed appropriate. Two were white women and one was a negress, age 42, 32, and 38; parities, 7, 5, and 10, respectively. The first two had had abnormal obstetric histories. Symptoms appeared, respectively, at the twelfth, thirteenth, and eighteenth weeks.

Blood pressure readings were excessively high, 270/100, 200/180 and 280/190. The eye grounds were mentioned in only one history. The pregnancies were terminated by abdominal hysterotomy and one by the vaginal route, abortion. The death certifications were chronic nephritis, malignant hypertension, and malignant nephrosclerosis.

All three cases came to autopsy with expected findings, in addition one showed septic infection following the therapeutic vaginal route abortion.

Here the symptoms were exaggerated in comparison to the previous group, the age level was higher, the parity greater, symptoms appeared earlier, blood pressure was on a higher level. The given diagnosis was more in line with the new classification.

A.II. Renal Disease

The second group of diseases not peculiar to pregnancy which stand in the background of toxemic symptoms during pregnancy is based on lesions of the kidney, acute or chronic.

Nephrosclerosis, A.II.a.

Among the histories examined there were 10 in which the diagnosis seemed to be chronic vascular nephritis or nephrosclerosis. These women had an average age of 29.2 years; an average parity of 3.9; and four had previous abnormal obstetric experiences. Two gave histories definitely suggesting previous abnormal cardiorenal systems.

In 6 cases, the symptoms were recorded as having appeared before the twenty-fourth week. In the remainder, late registration or indefinite history prevented accurate timing of symptomatology. Although the eye ground findings of three cases were recorded, it was noted that the terminology of description varied greatly. Because of the progress in ophthalmoscopic studies in the toxemias of pregnancy, there is no longer any excuse for failure to use a uniform terminology.

As in the hypertensive group, the fetal salvage was low; only 4 fetuses were born alive. Autopsies were performed in 6 instances. In the majority, a renal lesion was emphasized in the protocol. In 2 cases this old kidney pathology underlay a convulsive syndrome and in 1 a nonconvulsive termination.

In the certification of death 3 cases had been termed eclampsia, and in 2 additional cases toxemia was the final diagnosis.

Glomerulonephritis, A.II.b.

The second grouping of renal diseases included acute and chronic glomerulonephritis.

Acute Glomerulonephritis, A.II.b.1.—There were only 3 cases of acute glomerulonephritis in this series, less than 1 per cent. The average age of these women was thirty years, and the average parity was 2.6. Here the blood pressure was only moderately elevated, and the symptoms appeared early in pregnancy. The diagnosis on the death certificates corresponded with the new classification.

Chronic Glomerulonephritis, A.II.b.2.—The histories of 10 patients indicated they had suffered from chronic glomerulonephritis, A.II.b.2. Here the average age was twenty-nine years, and the average parity 3.3.

A definite history of a former renal lesion was present in half of these cases. Pyelitis had been previously present in 1, hypertension in 2, and obesity was noted in 4 cases. While the renal lesion predominated, the blood pressure curve was variable but tended to be high, all showed a maximum pressure of 170/100 except one, where the reading was 136/90. Symptoms were noted to have appeared before the twenty-fourth week in only 4 cases. Since prenatal care was adequate in only 3 cases, it is again felt that the value of some histories as to time of appearance of symptoms, may be questioned. Certification of death as due to nephritis occurred six times.

Autopsies were done in 5 instances, in 4 the findings were confirmative; in one a microscopic diagnosis of acute glomerulonephritis was made. Here some items of clinical course of this last case made us question whether the case might not have been one of eclampsia. In 5 cases toxemia dependent upon pregnancy had been present, and it was felt had been superimposed on a chronic renal lesion.

Marked albuminuria was not a striking characteristic in this group of 10 cases, but the sum total of history, symptoms, physical signs, and laboratory analyses seemed to indicate the presence of a primary chronic renal lesion. Only three fetuses were born alive in this group.

Nephrosis, A.II.c.

In but one case in the entire group did we feel the diagnosis of nephrosis, A.II.c., could be made from the evidence. The symptoms appeared early, the blood pressure continued low, and edema and albuminuria were pronounced. The patient died of shock from rupture of the uterus during a version and extraction. Possibly the degenerative process was seen early in its course, and did not have opportunity to change into a chronic glomerulonephritis.

Other Forms of Severe Renal Disease, A.II.d.

There were 9 cases which were undoubtedly renal in origin, but in which the histories and findings did not permit an exact grouping elsewhere in the new classification. The ages varied from 20 to 39, with an average of 25 years. Although the multiparas were in the minority, they had had many pregnancies.

The previous medical histories mentioned pyelitis in 2 primigravidas, nephritis of some type in 3, of whom 2 were primigravidas. One multipara had been treated for hypertension.

In at least 4 cases, symptoms had appeared before the twenty-fourth week. The blood pressure curves were variable, a wide range was noted in this group. In the autopsy protocols, pyelitis or pyelonephritis were mentioned for 6 cases.

In addition to grouping these cases as "other forms of severe renal disease" we felt one case might have had an added diagnosis of hypertensive disease.

Four fetuses were born alive and 5 were stillborn.

Summary of the Group

In reconsidering these histories from the standpoint of an effort to classify them according to the new grouping one encounters a number of difficulties:

1. In trying to determine whether the process is only in Group A or only in Group B; whether one is engrafted on the other; and whether the "A" syndrome makes "B" more likely.

2. Within Group "A" itself, in trying to differentiate from the records, often unavoidably incomplete, whether the case lies in Subgroup 1 or Subgroup 2.

3. Within the latter Subgroup 2, one encounters difficulty in differentiating hypertensive disease (A.I.), chronic glomerulonephritis (A.II.b.2), and chronic pyelonephritis (A.II.d.).

4. In view of current medical efforts to bring essential hypertension in relation to the kidney, it is confusing to separate chronic vascular nephritis or nephrosclerosis (A.II.a.) from hypertensive disease (A.I.a. and b.).

5. Chronic pyelonephritis has assumed such importance in the whole hypertensive-vascular disease problem that it would seem to deserve mention as such in the classification.

Group B: Disease Dependent Upon or Peculiar to Pregnancy

The second major subdivision of the new classification considers diseases dependent upon or peculiar to pregnancy; pre-eclampsia and eclampsia. The former is divided into mild and severe, the latter into convulsive and nonconvulsive (coma with findings at autopsy typical of eclampsia).

B.I. Pre-eclampsia

In the series studied, 63 cases, have been grouped as pre-eclampsia. Since all terminated fatally they were regarded as severe, B.I.b. There were 23 primigravidas, 36 per cent, and 40, 64 per cent who had had previous pregnancies. Twenty-four of the latter group gave histories of abnormal pregnancies, characterized by abortion, premature labors, stillbirths, or toxemias of pregnancy of various degree.

The medical histories showed varied previous or concomitant diseases: previous toxemia, 8; questionable toxemia, 1; hypertension, 8; chronic nephritis, 5; obesity, 8; thyroid disease, 1; diabetes, 2; cardiac disease, 1; previous pernicious vomiting of pregnancy, 1; previous puerperal infection, 2.

Although these women had serious pre-eclampsia, it is interesting to note the more definite cause of death, particularly from the obstetric angle. Thus 9 died of shock. This group includes one case certified as acute dilatation of the heart, which received a coroner's certificate of death as "due to shock." Two of the shock deaths occurred after

cesarean section (1 under spinal); two after version; one each after embryotomy, breech extraction, spontaneous delivery, a surgically induced labor; and one occurred during delivery.

The diagnosis of shock in itself as a cause of death is unsatisfactory. This diagnosis needs clarification as to the surrounding circumstances and mechanism, in the same way that emphasis is now placed on the differentiation of the various forms of the toxemias of pregnancy and the different forms of so-called essential hypertension.

Five patients died of post-partum hemorrhage. Twelve patients died of puerperal infection, in 8 cases the deliveries were spontaneous, in 4 the deliveries were operative, including 2 cesarean sections. In other words 26 of the 63 pre-eclampsia deaths were certified under joint causes which take precedence in the vital statistical grouping of puerperal deaths.

A close study of the material resulted in our separating this group of 63 cases from a mass of ambiguous and often misleading diagnoses. Among the diagnoses found obscuring a ready grouping under the new classification were such terms as acute and chronic nephritis, acute and chronic myocarditis, and acute dilatation of the heart, pulmonary embolism, sudden death, hepatitis, and inertia uteri, hepatic toxemia, cerebral embolism, surgical shock, uremia, malignant hypertension, secondary anemia, while the diagnosis of eclampsia occurred repeatedly although no convulsions had occurred.

There were 11 instances in which the classification might have been nonconvulsive eclampsia, but no autopsy record was available to establish the correctness of the latter grouping. Obviously in such cases there may have been an error in our selection of diagnoses. Again, 5 cases might have been hypertensive diseases, and 2 chronic glomerulonephritis, but the available history, findings, and the late appearance of symptoms and clinical course suggested more strongly the diagnosis of pre-eclampsia.

Autopsies recorded for 4 cases showed, in addition to lesions which pointed to pre-eclampsia, pyelitis in 1, chronic cardiac lesions in 2, and an acute endocarditis (puerperal infection) in 1.

Eight fetuses were undelivered, and 23 were stillborn in this group of fatal pre-eclampsia.

B.II. Eclampsia

Eclampsia was the evident cause of death in 156 cases—practically half the cases, 75 were primigravidas, 37 had had up to three previous pregnancies, while 44 had been pregnant four times or more. As to age groups, significantly more of these women were in the older brackets.

Convulsive Type, B.II.a.

There were 143 such cases. Prenatal care was regarded as none or inadequate in 109 cases. The adequacy of some of the remainder might be questioned. Four had a definite history of previous eclampsia, while the medical background included mention of 6 cardiacs, 18 with a suggestive renal disease history, 18 with obesity, 5 with hypertension, 6 each of syphilis, scarlatina, and pulmonary lesion, and 4 each of diabetes and thyroid disease.

The addition of other diagnoses such as terminal uremia, nephritis, and liver lesions which were really names of associated or terminal

conditions did not add to the clarity of the cause of death, but may have helped so often the sting of the true diagnosis stated alone. Necessarily the occurrence of a definite obstetric or surgical cause of death which takes statistical precedence must be included in a certificate of death. The varied diagnoses which were added to, or substituted for, the true cause of death in 52 certificates in this group of 143 convulsive type cases are shown in Table II.

TABLE II. DEATH CERTIFICATE DIAGNOSES IN CONVULSIVE ECLAMPSIA DEATHS

	NUMBER CASES
ECLAMPSIA (no other condition named)	52
ECLAMPSIA mentioned in connection with:	
Sepsis	1
Terminal uremia, nephritis	1
Acute yellow atrophy of liver	1
Secondary cardiac collapse	1
Chronic myocarditis	1
Acute cardiac dilatation	1
Acute toxic nephrosis, acute toxic degenerative hepatitis	1
Acute nephritis	3
Acute nephritis, hypertension	1
Nephritic toxemia	2
Nephritis	1
Chronic nephritis, uremia	1
Nephritis, pneumonia	1
Chronic nephritis	5
Pyelonephritis	1
Glomerulonephritis	1
Postoperative intestinal obstruction	1
Bronchopneumonia	1
Pre-eclampsia	1
ACUTE NEPHRITIS mentioned in connection with	
Lobar pneumonia, toxemia, pulmonary edema	1
Cerebral embolism, cardiac failure	1
Pulmonary edema	1
No other condition named	1
CHRONIC NEPHRITIS mentioned in connection with	
Uremia	2
Myocarditis	1
No other condition named	1
ACUTE HEMORRHAGIC NEPHRITIS AND THROMBOSIS AND UREMIA	1
NEPHRITIC TOXEMIA mentioned in connection with	
Uremia, fractured skull	1
No other condition named	1
NEPHRITIS WITH PERITONITIS	1
Toxemia and heart disease	1
Rheumatic heart, cerebral hemorrhagic, hypertension	1
Acute heart failure, hypertension	1
Pulmonary edema, acute cardiac dilatation, cloudy swelling of liver	1
Coronary thrombosis	1
Syphilis, terminal pneumonia, peritonitis	1
Acute yellow atrophy of liver	2
Hepatic toxemia	1
Uremia, pregnancy, metritis	1
Late toxemia, uremia	1
Kidney of pregnancy	1
Cerebral embolism	1
Brain abscess	1

From the angle of obstetric treatment, it was interesting to note the lowered incidence of infection, hemorrhage, trauma, and shock as causes of death in this group, when compared with the causes of death in the

pre-eclampsia group. The increased severity of this type of toxemia presumably did not afford opportunity for many obstetric maneuvers with their often serious consequences.

Low Blood Pressure Cases

Since the description of hypertensive encephalopathy by Oppenheimer and Fishberg, the tendency has been to attempt to correlate the convulsions of eclampsia with the height of the blood pressure. We must not forget, however that even though the patient is pregnant other causes for convulsions exist, for example, epilepsy, hypoglycemia and tetany, not to mention mass lesions of the brain and uremia. It is interesting that more than 8 per cent of our cases (twelve of 143 cases) of eclampsia developed convulsions with blood pressure below 150 systolic and 100 diastolic. In 5 cases the blood pressure readings were below 130/90, the point at which in most clinics the patient is usually regarded as sufficiently sick to warrant hospitalization for study.

Eclampsia, Nonconvulsive, B.II.b.

This group includes the nonconvulsive eclampsia (that is coma with findings at necropsy typical of eclampsia).

In reviewing the series, 13 cases appeared to come under this category. The causes of death as appeared on the certificates are appended in Table III. In connection with the single diagnosis of acute yellow atrophy of the liver, it may be said that jaundice in a toxemic pregnant woman does not necessarily justify such diagnosis.

TABLE III. DEATH CERTIFICATE DIAGNOSES IN NONCONVULSIVE ECLAMPSIA DEATHS

Acute toxic hepatitis	1
Cardiac and pregnancy	1
Chronic nephritis and acute dilatation of stomach	1
Pre-eclamptic toxemia, premature separation of placenta, post-partum hemorrhage	1
Paren. nephritis and pelvic peritonitis	1
Post-partum hemorrhage, abruptio placentae	1
Toxemia, anuria, uremia	1
Acute vasomotor collapse with post-partum eclampsia	1
Puerperal sepsis	1
Acute nephritis, chronic nephritis and toxemia of pregnancy	1
Toxemia of pregnancy, acute yellow atrophy of liver	1
Acute cardiac, post-partum hemorrhage	1
Pre-eclampsia	1

Six of the 13 women had abnormal obstetric histories; an additional one gave a history of previous hypertension; another of questionable nephritis; 1 was obese; 1 had had repeated streptococcal infections. The majority had typical symptoms which appeared late in pregnancy. The findings in 10 autopsy protocols were sufficient to make the classification definite. Three cases did not come to autopsy but the time of onset, the clinical course of the disease (coma), the laboratory findings, and blood pressure curve were so strongly similar to the other 10 cases that they could hardly be classified, except as eclampsia nonconvulsive in type.

There were several cases in which the clinical picture of an acute vascular collapse was seen. This was diagnosed in one case as acute vasomotor collapse with post-partum eclampsia (although no convulsions had occurred). Two cases termed acute cardiac dilatation and one termed acute dilatation of the stomach which were terminal mani-

festations in the nonconvulsive group were strongly suggestive of vascular collapse mechanism of death. Possibly one or two of the deaths in the pre-eclampsia group, which were ascribed to shock, may have come under this heading, as a rapid drop in blood pressure preceded in the fatal termination.

Attention has recently been called to several possibilities in the mechanism of death in states ordinarily called shock. Dexter and Weiss² place emphasis upon the administration of pituitrin as a factor in the circulatory collapse, while Steiner and Lushbaugh⁶ ascribe the collapse in some cases to amniotic fluid embolus. Young and McMichael⁷ call attention to a resemblance between obstetric shock from long labor and traumatic delivery, and the shock following renal failure after crushing of the limbs by fallen debris.

Summary

1. Thirty-six per cent of fatal cases of pre-eclampsia were primigravidas.

2. Sixty per cent of the multiparas had had previous abnormal pregnancies which indicate the importance of some morbid state, usually of the cardiovascular-renal system in the background of toxemia of pregnancy. These facts are brought out particularly in the taking of a detailed medical history. One of every six deaths were certified as due to shock; a diagnosis which in itself needs clarification.

3. The diagnosis of deaths from severe pre-eclampsia, as certified, are often ambiguous and misleading.

4. In attempting to classify such material as we have handled, the absence of autopsy findings renders it impossible to deal accurately with the group of pre-eclampsias in which we suspect nonconvulsive eclampsia.

5. The inadequacy of prenatal care in the eclampsia group reflects the now generally accepted viewpoint that such service and the opportunity for study and early treatment are essential in the prevention of toxemia of pregnancy.

6. There are probably other causes than hypertension for the convulsions in eclampsia. More than 8 per cent of our cases of convulsive eclampsia had a blood pressure of less than 150/100.

7. According to the new classification, nonconvulsive eclampsia may not be so grouped without autopsy findings. We were reasonably certain of this diagnosis in three cases which did not come to autopsy.

8. The unclassified group of toxemias of pregnancy will steadily shrink with more painstaking studies.

Group C: Vomiting of Pregnancy

Vomiting of pregnancy is listed in the new classification for the sake of completeness of the entire picture. Dieckmann,⁸ however, although a member of the committee which recommended the grouping, does not include this caption in his recent monograph on toxemias. Occasional attempts have been made to link this presumably toxic con-

dition of early pregnancy with the toxemias of later pregnancy, but no definitely related etiologic factor has been elicited.

There were 37 hyperemesis deaths in the series of 322 fatalities; over 10 per cent of the deaths resulted from toxemia with vomiting as the major symptom. Sixteen were primigravidas, 6 secundigravidas, 9 tertigravidas, and 5 in higher parities. Eight cases of the 20 with more than one pregnancy had abnormal obstetric histories, abortion, premature labor or stillbirths, 5 other cases had a background of previous toxemia of some degree. Four cases had presented a hypertension, 140/90 or more. Of these, three had had previous toxemia.

The diagnoses on the certificates of death were often bizarre and frequently misleading. The old diagnoses are presented in Table IV. Here again the naming of a terminal condition as a cause of death is an inexact medical practice.

TABLE IV. DEATH CERTIFICATE DIAGNOSES IN HYPEREMESIS GRAVIDARUM DEATHS

Hyperemesis gravidarum with:	
No other condition named	6
Acute nephritis	1
Profound toxemia	1
Early toxemia of pregnancy	1
Toxemia	1
Acute septic sinusitis	1
Bronchopneumonia	1
Acute cardiac dilatation	1
Toxemia with:	
No other condition named	8
Pernicious vomiting	1
Myocarditis	1
Cardiac failure	2
Bronchopneumonia	1
Pulmonary embolism	1
Acute yellow atrophy	1
Acute yellow atrophy with:	
No other condition named	2
Pyelonephritis	1
Nephritic toxemia	1
Toxemia and hyperemesis	1
Pernicious vomiting	1
Other diagnoses:	
Acute interstitial nephritis, acute cardiac congestion	1
Spontaneous abortion, degeneration of liver, pulmonary atelectasis, uremia	1
Pernicious vomiting, acute suppurative parotitis	1

Group D. Unclassified Toxemias

There were 13 cases, which because of insufficient or inconclusive data, could not be classified. Necessarily this final fatal illness precluded a follow-up, and unfortunately no autopsies were secured.

The final clinical diagnoses as recorded on the death certificates are shown in Table V.

Seven of these cases had maximum blood pressure readings of 130/90 or above. Three had edema, and 8 had albuminuria. Only 2 cases had abnormal obstetric histories, 2 had an history of rheumatic heart disease; and one additional case had both obesity and hypertension.

In two where death was ascribed to shock, the syndrome of vascular collapse peculiar to toxemia may have been present.

TABLE V. DEATH CERTIFICATE DIAGNOSES IN UNCLASSIFIED TOXEMIA DEATHS

Toxemia (hepatic)	1
Toxemia, carcinoma of ovary, cardiac and renal failure	1
Toxemia, acute nephrosis	1
Toxemia, with acute nephritis, acute myocardial degeneration	1
Toxemia, with acute hemorrhagic hepatitis	1
Post-partum puerperal eclampsia	1
Acute nephritis	1
Nephritis with valvular endocarditis	1
Uremia	1
Fatty degeneration, heart failure, peripheral cirrhosis collapse	1
Acute peritonitis with nephrosis	1
Uterine hemorrhage with cesarean section	1
Hyperemesis	1

Possibly some of the cases grouped here might have been properly classified with more painstaking histories, more complete physical examinations and eye grounds, and more appropriate laboratory analyses.

Conclusions

1. (a) The application of this classification to material such as we have studied was not entirely satisfactory. This was due in large part to the limitations of some of the material.

(b) We regard it as somewhat confusing to find the designation chronic vascular nephritis or nephrosclerosis (A.II.a.) under the heading renal disease, when it seems to us that it properly belongs in Group A.I., hypertensive disease. The authors of the classification allude to this fact, and we feel that the classification would be improved if this designation was placed in the hypertensive group.

(c) We believe that chronic pyelonephritis should be mentioned as such in the classification.

2. The attempt to apply this classification to the fatal cases of toxemia for ten years in Philadelphia has demonstrated to us even more forcibly than our previous experience suggested that patients with toxemia of pregnancy are not being studied as thoroughly as they should be.

3. Even though we have made a slight criticism of the classification we feel that its adoption by hospitals and clinics will do much toward the understanding of the toxemias of pregnancy and the reduction of maternal mortality from this cause.

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CLINICAL EXPERIMENTS IN RELATION TO THE EXCRETION OF THE ESTROGENS*

III. Urinary Estrogens in a Normal Menstrual Cycle and in a Case of Essential Dysmenorrhea

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NUMEROUS investigators have measured total urinary estrogens throughout normal menstrual cycles and have reported curves in general agreement with published^{6, 11, 18†} and unpublished results from this laboratory. Increased excretion has been consistently found during the luteal phase of the cycle with a marked premenstrual drop to low levels which are maintained during flow. In some cycles we and others have noted two peaks of excretion during the intermenstrual period. Data on separated urinary estrogens throughout menstrual cycles, however, are extremely limited.^{6, 11, 19} The present investigation was undertaken with the purpose of supplementing these observations on cyclic changes in the partition of urinary estrogens and of gaining more information concerning estrogen destruction by determining also the T_{24} to T_0 ratios and the "unaccounted for" T_{24} activity of specimens.‡

One of these women, Mrs. E. H., aged 37 years, had had a perfectly normal menstrual history since puberty at the age of 13, with two normal pregnancies and little or nothing in the way of menstrual molimina since her first child, seven years before the time of this study. The other, Miss A. R., aged 26 years when the first cycle was followed, had had fairly regular but consistently painful periods since puberty at the age of 12. The amount of pain varies but is always disabling on the first day of flow. Thyroid extract, taken for a year before these studies were made, had no apparent effect upon the dysmenorrhea. No pelvic or organic abnormality to account for the pain has been discoverable in the five years that she has been under our observation.

Normal Menstrual Cycle. Mrs. E. H. (Chart 1)

The total estrogenic potency (T_0) of urine in this cycle follows the usual normal curve. A higher level of excretion might have been detected if a specimen had been assayed between the fifteenth and twentieth days, since it is during this interval (around twelve days before the onset

*Presented, in brief, at a meeting of the New York Obstetrical Society, January 13, 1942.

The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee on Research in Problems of Sex of the National Research Council.

†See references in fourth paper of this series.

‡For the methods employed, explanation of the terms used, and interpretation of findings, the reader is referred to the first paper of this series.

of menstruation) that we have usually found the peak in total estrogen excretion.¹⁸ The fourteenth through the twenty-first day of this twenty-eight-day cycle covers the period of maximum excretion of estrogens, the potency of all three fractions being greatest at this time. When total estrogens are calculated in terms of weight (micrograms) rather than activity (I.U.), this increased excretion during the luteal phase over that at the time of menstruation is even more striking, the reason being that during menstruation most of the estrogenic potency of the urine is accountable to α estradiol, which has ten times the activity of either of the other two.* The fourteenth to the twenty-first day of this cycle also covers the period of maximum conversion of estradiol to estrone to estriol, as shown by the partition of the separated estrogens, and of minimum destruction, as indicated by the low T_{zn} to T_0 ratios, the small amount of "unaccounted for" T_{zn} activity and the increased recovery of estrone, the most labile of the three urinary estrogens. These findings

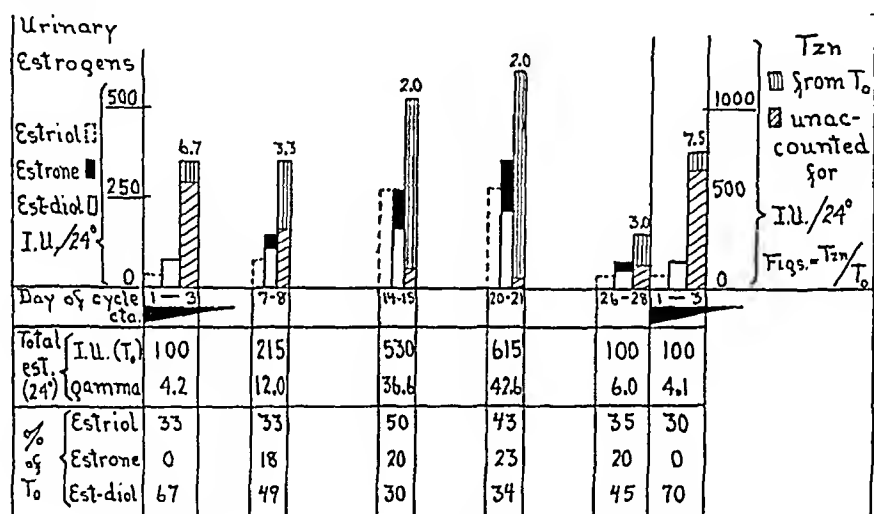


Chart 1.—Mrs. E. H. Normal menstrual cycle.

are all in keeping with our repeated observation that progesterone prevents destruction and facilitates conversion of secreted estrogen. In fact, the urinary changes signify some luteal activity as early as the seventh day of this cycle, almost certainly before ovulation, thus supporting other indirect evidence that secretion of progestin precedes ovulation.²⁰⁻²³ It has been generally accepted that the maximum secretion of estrogen as well as progestin occurs during the luteal phase of the normal cycle, so that increased secretion as well as decreased destruction may contribute to the higher levels of urinary excretion at this time.

It is interesting to speculate concerning the rate of estrogen secretion in this normal cycle. In five experiments to date,† separated estrogens and T_{zn} values have been determined before and after the administration of either estrone or estradiol. The urinary recovery of the injected estrogens (by weight) has varied between 2 and 14 per cent, depending apparently upon a number of factors which are discussed in the first and

*See first paper of this series (September, 1942, issue) for standardization values of crystalline estrogens by our assay technique.

†Two of these are reported in this series of papers (Chart 1, Paper I, September, 1942, issue, and Chart 4, Paper II, October, 1942, issue). One was reported in 1938,⁶ although the T_{zn} values were not included. The other two are unpublished.

second papers of this series. In each experiment the "unaccounted for" activity after zinc-hydrochloric acid hydrolysis has borne a more constant relationship to the quantity of hormone administered, amounting to 5 to 10 per cent of the activity of the "lost" estrogen. On the basis of these findings, we might calculate the approximate rate of estrogen secretion during this cycle by assuming that the "unaccounted for" T_{zn} activity represents 10 per cent of the destroyed secreted estrogen. For example, in the first specimen from Mrs. E. H., 595 I.U. per twenty-four hours of the total activity after zinc-hydrochloric acid hydrolysis were "unaccounted for" by the active estrogens excreted. This would represent 5,950 I.U. of destroyed estrogen. Adding the 100 I.U. per twenty-four hours of active estrogens found in the urine, we get 6,050 I.U. as the amount of estrogens secreted daily during these first three days of menstruation. Similar calculations throughout the cycle give values between 860 and 6,600 I.U. with an average of 3,300 I.U. per twenty-four hours. These figures, of course, are based on a number of as yet unproved assumptions and are not presented as anything more than speculative. It is interesting, however, that Corner,²⁴ attacking the problem of ovarian secretion of estrogens from an entirely different angle, namely, the amount necessary to reproduce normal function in the castrate monkey, arrived at 3,000 I.U. as the average daily level of secretion by the normal human female, and W. M. Allen, quoted by Corner,²⁴ estimated, from clinical experiments on women, that 4,200 I.U. of estrogen are secreted daily.

One intimation arises from our calculations which is contrary to the usual conception of cyclic ovarian activity and which may or may not prove to be fallacious, namely, that the most rapid secretion of estrogenic substance comes during the first three days of the cycle and is greater during the follicular than the luteal phase.

In a previous publication⁸ we advanced the theory that estrogen breakdown products rather than estrogens per se, either directly or through the pituitary, stimulate luteal secretion, and that the peak of corpus luteum activity may, through reducing estrogen destruction, bring about its own regression. The specimen collected on the twentieth and twenty-first days of this cycle contained only 25 I.U. of "unaccounted for" T_{zn} activity, indicating that a minimal amount of degradation of secreted estrogen was occurring. This comparative deficiency of estrogen breakdown products may be responsible for the gradual regression of luteal activity which precedes menstruation. With the resultant decrease in progesterin would come a gradual increase in estrogen degradation (as indicated by the higher T_{zn} to T_o ratio and the increment in "unaccounted for" T_{zn} activity in the specimen collected over the last three days of the cycle), thus providing a stimulus synergistic with follicle stimulating hormone for the start of new follicular growth.

The sudden shift in the partition of urinary estrogens at the start of menstruation and the marked increment in the amount of activity which may be recovered by zinc-hydrochloric acid hydrolysis have been previously reported and discussed.^{2, 6} A striking increase in the rate of estrogen destruction is indicated, and we have suggested⁶ that a sudden

concentration of estrogen breakdown products in the endometrium may result in the formation of a local "toxin" whose action is directly responsible for menstruation. Markee has intimated from his extensive studies that the causative factor in endometrial bleeding must be a local one.²⁵ Although we have found a "toxin" in menstrual discharge,²⁶ we are not satisfied, by our studies to date, that estrogen breakdown products are chemically involved in its formation. That withdrawal of hormonal support is a consistent forerunner of endometrial bleeding has been convincingly demonstrated. In our urinary studies evidence of a precipitous shift in steroid metabolism, characterized by a rapid increase in estrogen degradation, has consistently followed estrogen and progesterin withdrawal. Although these two phenomena must in some way be intimately related, the toxin which we believe causes menstruation may well come from the changed metabolism of the endometrium itself, consequent upon steroid withdrawal rather than from any products of steroid degradation.

In the preceding paper of this series we have good circumstantial evidence that estrogen and progesterone withdrawal bleeding provides a necessary stimulus for the normal growth and maturation of the ovarian follicle which may not be provided by simple estrogen withdrawal flow. The *precipitous* change in steroid metabolism which characterizes post-ovulatory menstruation, with its concomitant *sudden* marked increase in estrogen degradation, may well supply the essential factor for this complete follicle stimulation.

Essential Dysmenorrhea. Miss A. R. (Chart 2)

Estrogen excretion has been studied in three of this individual's cycles and the similar results in each point to marked deviations from the normal, if the data on Mrs. E. H., Chart 1, and the other two normal cycles in which separated estrogens have been measured^{6, 11} may be considered representative of the normal. Whether or not the deviations are characteristic of essential dysmenorrhea must await further investigation.

In the 1939 part of this study zinc-hydrochloric acid hydrolyses were not performed, an omission which detracted considerably from the value of the findings. Furthermore, the results on separated estrogens are presented with some reservations as to their quantitative accuracy since only forty-eight-hour specimens were worked up before this individual was found to have very low estrogen output. Despite the smaller amounts of material for assay, the level and curve of total estrogen excretion are practically the same as found during the same period of two cycles subsequently studied, during which seventy-two-hour collections were analyzed.

A comparison of the figures in Chart 2 with those in Chart 1 reveals that a decidedly low output of known estrogens is associated with a

relatively high output of "unaccounted for" potency from zinc-hydrochloric acid hydrolysis. This would signify greater destruction of secreted estrogen and hence deficient progestin activity through the cycle.

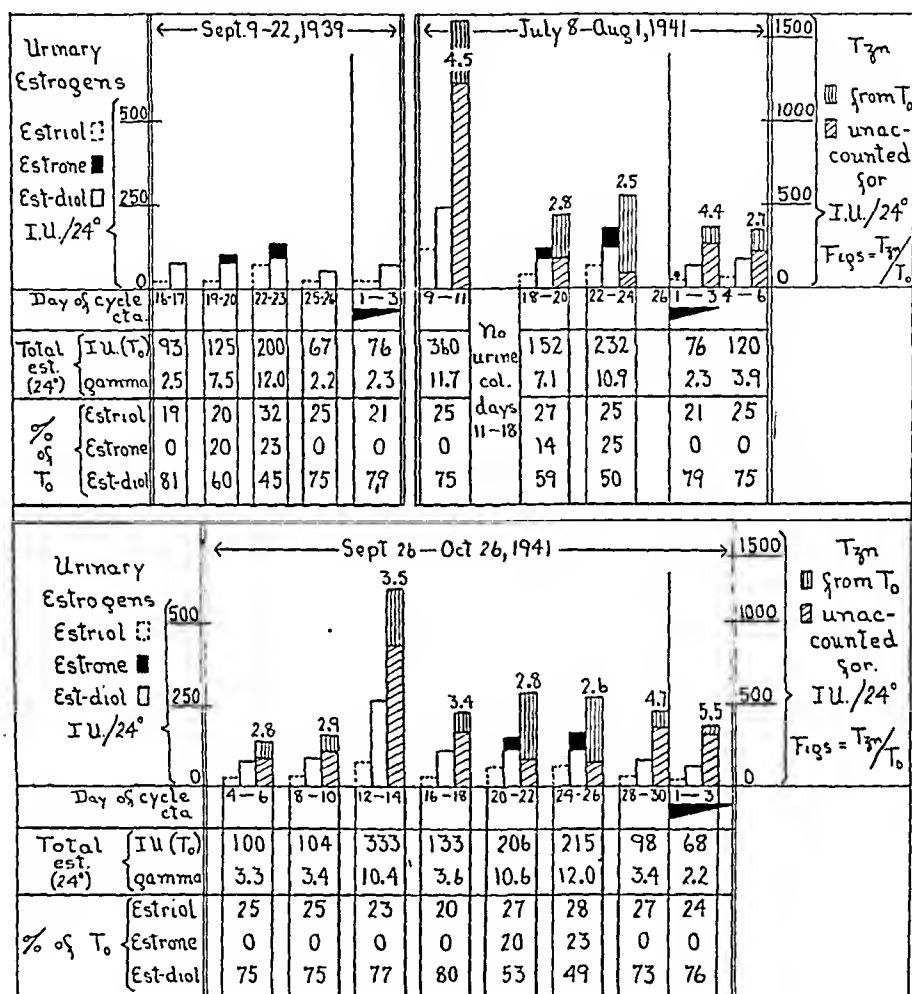


Chart 2.—Miss A. R. Essential dysmenorrhea.

If we may speculate again, we would conclude that there is no deficiency of ovarian secretion of estrogenic substance in this patient. Calculations, based on the assumption that "unaccounted for" T_{zn} activity represents 10 per cent of destroyed estrogen, give daily secretion values from 1,100 to 9,000 I.U. and an average of 3,760 I.U. as compared with an average of 3,300 I.U. in Mrs. E. H., the normal case reported above.

The values form a two-peak curve of total estrogen excretion during the intermenstruum. Two-peak curves have been reported without any associated dysmenorrhea.^{11, 27} In one such cycle of a normal individual, however, the results of partial separation of urinary estrogens indicated that luteal secretion started with the first increase in output of total estrogen, fourteen to sixteen days before flow.¹¹ The first peak in

estrogen output by Miss A. R. also comes when advanced follicular development would be expected, sixteen to nineteen days before the next period. The greater excretion of estradiol and of "unaccounted for" T_{21} activity at this time indeed reflect increased secretion of estrogen, but these changes are also indicative, accompanied as they are by absence of estrone,* no rise in the percentage of estriol, and high T_{21} to T_0 ratio, of no accompanying increase in luteal effect. We must conclude, therefore, that this individual differs from the normals we have studied in that there is no urinary evidence of luteal development during the follicular phase of the cycle.

In fact, no evidence of any increase in luteal effect upon estrogen metabolism is found up to the time, eleven to nine days before menstruation, when the second rise in total estrogen excretion began. This second peak, although less marked than the first in activity units, is actually of the same order when total estrogens are calculated in micrograms. The appearance of estrone at this time, the drop in estradiol, the rise in estriol, and the decrease in "unaccounted for" T_{21} activity all indicate that this patient does have some luteal secretion during the second half of the cycle. Whether or not this change is postovulatory can only be surmised. The finding of pregnanediol in the urine has commonly been accepted as evidence of ovulation. Analyses for urinary pregnanediol in the September, 1939, twenty-seven-day cycle of Miss A. R. revealed its presence, in small amounts, from the eighteenth through the twenty-fourth day. As early as 1926, however, partial luteinization of an unruptured follicle containing an ovum was reported by Stieve,²⁸ and Venning and Browne²⁹ in referring to this observation point out the possibility of luteal development, and hence pregnanediol excretion, without ovulation. If this patient ovulates at about the middle of her cycles, why do our urinary studies fail to reflect luteal secretion until some days later? If ovulation occurs as late in the cycle as we find evidence of progestin activity, why is menstruation not postponed? Delayed, deficient, and short-lived luteal development appears to be the answer.

We would conclude that this individual bleeds upon progestin withdrawal, but that her premenstrual preparation, at least so far as luteal effect upon estrogen metabolism is concerned, is subnormal. There is convincing evidence from morphologic studies^{30, 31} that functional dysmenorrhea requires the presence of a secretory endometrium. If deficient luteal development is characteristic of this disorder, it seems that a poorly developed progestational endometrium would have been observed in these cases. Either this ease of ours is atypical or the quantitative deficiency revealed by our studies is not accompanied by any morphologically demonstrable deficiency in secretory development.

*Assay of estrone by our method (see first paper, September, 1942, issue, of this series) might give falsely negative values in urines of very low estrone and estradiol content, but the absence of estrone in the urines collected at the time of the early peak in T_0 is definitely significant.

Although menstruation itself, in Miss A. R., is associated with an increased rate of estrogen degradation, the metabolic shift at this time is less pronounced than was observed in Mrs. E. H. and in the two other previously reported normal cycles in which T_{zn} to T_o ratios were followed.^{2, 32} In this and the second paper of this series it was proposed that the sudden marked increase in estrogen degradation, which pertains at the onset of normal postovulatory menstruation and which characteristically follows the withdrawal of estrogen and progestin, may provide an essential factor for complete stimulation of the beginning follicle. In the cycles of Miss A. R. it is possible that a comparative deficiency in luteal function, followed by a less marked metabolic shift upon its withdrawal and the start of flow, may result in a comparative deficiency in follicle stimulation which accounts for the subsequent abnormalities in follicle growth and maturation as indicated by our estrogen studies.

Following this same line of thought, that estrogen degradation is a factor in ovarian stimulation, one wonders why luteal development should be deficient in a patient who shows, throughout the cycle, evidence of excessive destruction of secreted estrogen. A striking increase in the amount of "unaccounted for" T_{zn} activity accompanies the first peak in estrogen output. Why should this fail to provide the required ovarian stimulation? It is possible that the timing of this stimulation in relation to the state of growth of the follicle is important. In the normal cycle this sudden increase in degradation coincides with the start of menstruation when new follicular growth is supposedly just beginning, whereas in this individual the follicle is presumably well under way by the time any marked rise in the level of estrogen degradation products is apparent.

Some indication of a relationship between the luteal deficiency in this case and her dysmenorrhea has been provided by the results of therapeutic trials. Two completely painless periods have followed the administration of estrogen according to the technique recommended by Sturgis and Albright.³¹ These were presumably simple estrogen withdrawal flows and the symptomatic relief is in accord with their conclusion that secretory development is an essential precursor of painful menstruation. Another practically painless period in this individual, however, and one that was considerably more normal in amount, followed the daily ingestion of 15 mg. of estriol starting on the fourteenth day of the cycle. Menstruation was forestalled until the fortieth day, two days after the last dose. That the luteal phase was prolonged was indicated by the finding of pregnanediol in two twenty-four-hour specimens of urine, one collected on the thirty-first and another on the thirty-fifth day. The symptomatic relief in this instance was in keeping with the assumption that deficient luteal effect may in some way be responsible for this patient's complaint.

Summary and Conclusions

Urinalyses during a normal menstrual cycle for separated estrogens and for the additional estrogenic potency which results from zinc-hydrochloric acid hydrolysis of specimens have confirmed our repeated observations concerning the effect of progestin on estrogen metabolism, have indicated that some luteal activity normally precedes ovulation, and have supplied additional information which points to a physiologic role of estrogen degradation in the regulation of cyclic ovarian secretion.

Similar studies during three cycles in a case of essential dysmenorrhea have indicated that this patient differs from the normal case herein reported and from two other normals previously studied in that estrogen excretion is extremely low, due to a comparative deficiency in luteal effect throughout the cycle. Two intermenstrual peaks in estrogen excretion appeared, but not until the start of the second rise, nine to eleven days before the period, was there any evidence of progestin effect upon estrogen metabolism. Furthermore, the shift in steroid metabolism at the start of flow, pointing to a sudden increase in the rate of estrogen degradation, was less marked in this individual than in the normals. This may be of significance in relation to the indicated subsequent comparative deficiency in normal growth and maturation of the ovarian follicle.

The findings and the results of hormone therapy suggest that subnormal luteal activity with consequent incomplete premenstrual preparation may be of etiologic significance in this particular case of essential dysmenorrhea.

Lapin, Joseph H.: Dermatitis Due to "Antiseptic Oils," *Am. J. Dis. Child.* 63: 89, 1942.

The writer saw six children under three months of age on whom "antiseptic baby oil" had been used since discharge from the maternity ward. The torso and limbs had been bathed in soap and water but the face had been cleaned with nothing but the oil. These infants showed a patchy, erythematovesicular dermatitis, with occasional papules. The dermatitis was practically limited to cheeks and forehead. A patch test showed, after application for forty-eight hours, erythematous and vesicular lesions.

The offending substance in such oils probably is hydroquinone used as an antioxidant.

HUGO EHRENFEST

CLINICAL EXPERIMENTS IN RELATION TO THE EXCRETION OF THE ESTROGENS*

IV. The Effect of Veratrum Viride Upon Urinary Estrogens in Pre-Eclampsia

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IN A recent study⁸ of urinary steroids during spontaneous and induced labor, a striking change in the excretion of estrogens and pregnanediol was reported, this effect being presumably due to embarrassment of placental circulation by uterine contractions. It was of interest to determine whether or not an opposite effect on blood supply would result in opposite changes in steroid metabolism as reflected in the quantification of their excretory products. The opportunity for such a study was offered when one of us (A. G. G.) decided to administer veratrum viride to a patient whom he had sent to the Boston Lying-in Hospital during the thirty-second week of pregnancy because of severe pre-eclampsia superimposed on essential hypertension.

Methods

The methods of urinalysis were the same as described and referred to in the first paper of this series. Each voiding during the period of study was saved and the time covered accurately recorded.† Urinary albumin was quantitatively measured in each specimen. For estrogen assay, up to the time when veratrum was administered, twelve-hour specimens from 7 P.M. to 7 A.M. were pooled. During veratrum injections shorter intervals were covered. All results are expressed in terms of twenty-four-hour excretion for the sake of comparison.

Experimental Study

Mrs. H. M., a 23-year-old gravida i, was first seen in September, 1940, when three months pregnant. Her blood pressure at the time was 149/90 and remained at about this level, with no other abnormal signs or symptoms until Jan. 20, 1941, when she was thirty weeks pregnant. A very slight trace of urinary albumin was then observed; blood pressure had risen to 155/90; there was some ankle edema and she had gained five pounds in two weeks, despite dietary restrictions. Ten days later she was admitted with a blood pressure of 160/105, a slight trace of urinary

*Presented, in brief, at a meeting of the New York Obstetrical Society on January 13, 1942.

The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee on Research in Problems of Sex of the National Research Council.

†Collections were supervised by the patient herself, to whom we are indebted for unusually intelligent and careful cooperation. Creatinine determinations on each specimen indicated that no losses or errors in timing had occurred.²

albumin, and marked edema of the legs, hands, and face. Weight on entry was 150 pounds, a gain of 28 pounds during the pregnancy. She was given a low salt, high protein diet with fluids restricted to 1,500 c.c. and magnesium sulfate catharsis. During the first three days she lost three pounds, but still had facial edema. Blood pressure and urinary albumin were unchanged.

The total estrogenic potency of the urine collected over twelve hours on the night of entry into the hospital was within the limits of normal for this period of gestation (10 mg. per twenty-four hours in estrone equivalents). However, there was an abnormally low percentage of estriol, a high percentage of estradiol, no demonstrable estrone, and a high ratio of activity after zinc-hydrochloric acid hydrolysis (T_{zn}) to the total activity after the usual hydrochloric acid hydrolysis (T_o). A second specimen collected after three days of the above regime showed the same picture. This partition of urinary estrogens, a consistent finding in patients with pre-eclampsia and eclampsia,^{6, 7, 9} is interpreted as reflecting a decrease in the rate of estradiol to estrone to estriol conversion (that is, a progestin deficient metabolism) together with rapid degradation of secreted estrogen.

Progesterone and Estrogen Treatment.—From February 4 to 9, inclusive, she received daily injections of 10 mg. of estradiol benzoate and 25 to 50 mg. of progesterone* together with 50 to 100 mg. of pregnanediol glucuronide by mouth. The clinical and hormonal changes during this time were entirely similar to those observed in 7 other previously reported cases of severe pre-eclampsia similarly treated.¹⁰ After three days there was evidence of a more normal steroid metabolism, blood pressure had dropped to 140/80, half as much albumin was being excreted, and visible edema had disappeared. By the sixth day of treatment, however, a recrudescence of both the clinical and hormonal abnormalities was apparent, despite an increase in the amount of progesterone administered.

Adrenal Cortical Extract.—From February 10 to 13, inclusive, 20 to 75 c.c. of adrenal cortical extract† were given daily together with the same amounts of estradiol benzoate and progesterone. A progestin-like effect of adrenal cortical extract upon estrogen metabolism had been previously reported.¹⁰ This observation was confirmed after the first day of Eschatin administration when 75 c.c. were given intravenously. There was a 100 per cent increase in estriol excretion, a corresponding rise in urinary estrone, and a marked drop in the T_{zn} to T_o ratio. This effect was not maintained, however, by continued injections. Estriol excretion steadily decreased and, in the urine collected from the thirteenth to fourteenth of February, estrone was barely demonstrable and the T_{zn} to T_o ratio had risen, both indications of more rapid estrogen destruction. No injections were given on the fourteenth. In the twelve-hour specimen from 7 P.M. to 7 A.M., February 14 to 15, no estrone was demonstrable, estriol was lower, and the T_{zn} to T_o ratio higher than in the admission urine before therapeutic trials with estrogen, progesterone, and adrenal cortical extract. Albuminuria during these thirteen days had increased from 0.3 to 1.9 Gm. in twenty-four hours, hypertension from 160/105 to 180/116, and weight had returned to 150 pounds.

*Progynon-B and Proluton, products of the Schering Corporation.

†Parke, Davis & Company Eschatin, bought from funds supplied by Miss Florence Willis.

tardation of heart rate, extreme nausea, vomiting, diarrhea, and sweating. The urinary values covering ten to fourteen hours after the last injection were back to the pre-injection levels. As is well known, the clinical response to this drug is also of short duration.

The urines collected following treatment on February 16 and 17 showed less marked deviations. This may have been partly due to less heroic administration of veratrum. Furthermore, ten-hour rather than four-hour collections were pooled for these determinations and toward the end of this period urinary changes had undoubtedly disappeared.

On February 18 no veratrum was given until 7 P.M. A four-hour specimen collected in the afternoon showed pre-injection levels and partition of urinary estrogens, thus supplying a control observation for the afternoon excretion during veratrum injections on February 15, and demonstrating that the urinary changes resulted from injections and not from any hourly fluctuations in estrogen metabolism. By 7 P.M. the blood pressure was 190/130. Eight minims of veratrum caused an immediate drop and the same changes in estrogen excretion as previously observed, this effect completely disappearing five hours after the injection. The urine collected from 1 to 9 A.M. the next morning reflected the pre-injection picture of estrogen degradation and failure in conversion. At 9 A.M. on February 19 a cesarean section was performed and a four-and-one-half-pound baby delivered, which survived. Two months after delivery the patient's urine was albumin-free, but her blood pressure was still elevated to 180/90.

The variations in albuminuria during veratrum treatment are difficult to interpret. There is some indication that the immediate effect of the drug was to cause an increased output, especially since no such rise in late afternoon and evening specimens was apparent prior to veratrum administration. The markedly increased excretion during the day on February 18, when no injections were given, however, would indicate that, except for short intervals of increased output, albuminuria was somewhat controlled by the therapy. The depressant effect of the drug upon hypertension needs no comment other than that, as noted by others, its action is of short duration.

Discussion

The observations reported above together with the previously published findings in spontaneous and induced labor would seem to supply unquestionable evidence of a direct effect of vascular supply upon steroid metabolism. That vasodilatation raises the level of circulating estrogens is apparent. How much of this increase is accountable to greater production and how much to lessened destruction cannot be ascertained from this experiment. In any event the resultant increase in the rate of estradiol to estrone to estriol conversion provides another example of how this conversion mechanism is favored by any condition that retards steroid degradation.

A natural inference might be that the changes in the urinary excretion of estrogen and progestin metabolites which we have been reporting in pre-eclampsia and eclampsia are a result of vasoconstriction rather than causally related to the disease. Changes in the placental hormones prior to the development of any clinical signs of toxemia,

however, have been demonstrated. In a total of 32 pre-eclamptic patients to date, January, 1942 (4 unreported), an abnormal rise of chorionic gonadotropin in the serum has been detected four to eight weeks before there was any clinical evidence of abnormality.⁹ In the 6 patients to date (2 unreported) in whom the separated urinary steroids have been followed prior to the development of clinical manifestations, toxic signs were preceded by evidence of disturbed steroid metabolism, the findings indicating a progressive deficiency of estrogen and progesterone.⁹ That estrogen deficiency precedes pre-eclampsia has been indicated also by the finding of low levels of estrogenic activity in the serum before as well as during the disease.^{7, 33}

In all of our studies of estrogen and progesterone metabolism in both pregnant and nonpregnant women, evidence of estrogen and progesterone withdrawal has been consistently followed by the striking shift in excreted estrogen metabolites which characterizes the onset of pre-eclampsia, of labor, and of menstruation, and which reflects a rapid increase in the rate of estrogen degradation. That the local vascular changes of the menstruating endometrium are the ultimate effect of changes in ovarian steroids is incontrovertible. It is reasonable to assume that similar changes in the female sex steroids preceding pre-eclampsia result ultimately in the generalized vascular disturbances of this disease.

The concept is tenable, therefore, that a reciprocal relationship exists between the vascular system and female sex hormones. Adequate sex steroids are known to be essential for adequate genital vascularity. Adequate vascular supply appears to be equally important for the proper production and metabolism of the placental and ovarian steroids. This concept implies that among the primary causes for pre-eclampsia and eclampsia may be included any mechanical or organic disturbance which affects adversely the blood supply to the placenta. Thus, in the case herein reported, in which severe pre-eclampsia was superimposed upon essential hypertension, the circulatory disturbance manifested in the hypertension itself may have been primarily responsible, through restricting the vascular supply to the growing products of conception, for a deficient production of placental steroids. The resultant changed metabolism of estrogen and progesterone may have augmented the vascular deficiency, and the final marked increase in the severity of toxic signs may have been evidence of the establishment of a vicious circle in which steroid degradation and vasoconstriction were augmenting one another.

According to this concept the logical point of attack in the treatment of pre-eclampsia and eclampsia is to cut in upon this circle either by replacement therapy with estrogen and progesterone or by directly combating the vasoconstriction. The limitations of the former point of attack in severe pre-eclampsia are apparent from the results in this case and

in others previously reported.¹⁰ The principal drawbacks to the use of veratrine in combating vasoconstriction would appear to be the relatively short duration of its action and the toxic side effects. In the hands of the group at the Cincinnati General Hospital,³⁴ the use of veratrine in controlling pre-eclampsia and eclampsia until the pregnancy could be safely interrupted has been strikingly successful. The possibility of supplementing sex steroid therapy with veratrum viride administration deserves investigation. According to the above concept, the effectiveness of each might be prolonged and enhanced so that smaller dosages of both would be required to counteract the circulatory and hormonal abnormality.

Summary

Urinary studies in a patient with severe pre-eclampsia during a four-day period when veratrum viride was given have shown that the excretion of estrogen metabolites is markedly affected by the temporary vasodilatation caused by this drug. The findings indicate a sudden decrease in degradation and increased metabolic conversion of the estrogens. The hormonal effects are of as short duration as are the clinical. There is reason to suppose that the relationship between sex steroid production and metabolism and genital vascular supply is reciprocal. The etiologic and therapeutic implications of this finding are discussed.

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END RESULTS OF THE RICHARDSON COMPOSITE OPERATION FOR UTERINE PROLAPSE

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THERE is as yet no uniformity of opinion concerning the best method of treatment of uterine prolapse and the attending conditions commonly found associated with it. The conditions to which we refer are disease of the cervix, cystocele, urethrocele, stress urinary incontinence, rectocele, enterocele, relaxed vaginal outlet, and benign disease of the corpus uteri. It is desirable that one should not have a fixed mind in approaching this problem, for each case should be carefully judged and treated in a manner the surgeon considers most fitting to that individual patient. We are excluding from consideration those cases of prolapse occurring in women in whom the function of future childbearing is desirable. It is our opinion that these are best treated by the combined procedure of a suitable plastic vaginal repair coupled with some type of intra-abdominal suspension. During the past several years combined vaginal and abdominal procedures have given way to vaginal operations of different types in almost all clinics in those cases in which future childbearing is impossible or undesirable. We feel that this indicates a definite progressive step in surgical technique, for it is obvious to most experienced gynecologists how much more easily those of advanced age go through operations of the vaginal type than those in which laparotomy is done.

Notwithstanding what has been said concerning the desirability of individualizing each case, various clinics have had a tendency to utilize favorite operations for prolapse and associated conditions. In one, the vaginal hysterectomy is done almost routinely, in another, the Watkins interposition and in a third the Manchester operation in its various modifications. The majority of operators in our clinic have used the Watkins interposition operation rather extensively for prolapse of second and third degree. We have been rather conservatively inclined toward vaginal hysterectomy, using it chiefly in those cases of prolapse in which benign disease of the corpus uteri makes it desirable to remove the organ. Follow-up studies on women upon whom the Watkins interposition had been done were made by Brady¹ and later by Everett.² Both showed excellent end results as far as cure of the prolapse is concerned. Everett's figure for cure was 96 per cent and in no case in which there was a complete prolapse was there a recurrence. This would seem to answer effectively the objection of some to the interposition operation in

cases of complete descensus. Everett also found that in 30 per cent of the women upon whom a vaginal hysterectomy was done there was an unsatisfactory anatomic result. These anatomic failures were due to recurrent cystocele, prolapse of the vaginal vault and in one instance to the development of a large enterocele. This incidence of unsatisfactory anatomic results is higher than in most reported cases of vaginal hysterectomy for the reason that the group included only cases of marked prolapse. It is obvious that when vaginal hysterectomy is done, frequently, as in some clinics, for small fibroids, functional bleeding and retroversion of the uterus, there will be much less tendency for the vagina to prolapse or for cystocele to occur.

Notwithstanding our excellent results in curing uterine prolapse with the interposition operation, we confess that the operation has certain shortcomings. If the uterus is interposed in relatively young women, there are many years ahead in which myomas, functional bleeding, or even corporeal carcinoma may develop. Even if done after the menopause the latter condition may develop and the removal of the uterus after it has been adherent to the vaginal wall is attended with much technical difficulty. If the fundus of the uterus is fixed well up under the pubic arches the anterior wall of the vagina is often shortened and in any event the anterior vaginal wall is fixed and the organ is not as pliable as is desirable.

The Manchester operation has enjoyed some popularity in this country following Shaw's³ address before the American Gynecological Society in 1933. It is nothing more than a radical anterior colporrhaphy coupled with a cervical amputation and posterior colporrhaphy. The operation has been variously modified in different clinics in this country but not fundamentally changed. It does very well in the cure of cystoceles with first- and, at times, even second-degree descensus, but it hardly seems a logical procedure when there is a complete procidentia. It has the advantage of being the simplest and least shocking of the various operations for cystocele and prolapse. This is a real advantage in women of advanced age who are none too good surgical risks.

Because of his dissatisfaction in some respects with the above-named procedures, Richardson, Sr., began, several years ago, to seek a new method of curing uterine prolapse. The composite operation which he devised combines the admittedly desirable features of vaginal hysterectomy with those of the transposition methods. His operative plan had as its objective "(1) riddance of the hypertrophied and diseased vaginal portion of the cervix; (2) extirpation of the corpus uteri, together with the tubes and ovaries if indicated; (3) optional destruction or excision of any remaining cervical canal epithelium; (4) minimal trauma and devitalization of structures later to be utilized for reconstruction purposes; (5) preservation of an assured and adequate blood supply to these several units; (6) total ablation of associated enterocele through high

obliteration of the cul-de-sac of Douglas; (7) rational utilization of all supporting structures that experience has demonstrated to be helpful and dependable; namely, the pubocervical fascia, the basal portions of the broad ligaments with their extraordinarily strong cervical attachments, the uterosacral and the round ligaments, the fascia of the rectovaginal septum, as well as the muscles and fascial layers of the pelvic floor and perineum; (8) re-establishment of a vagina of normal depth and caliber; and (9) restoration of normal anatomic relationships.”

The technique of the Richardson composite operation has been described in detail by its author, but since the procedure is a new one which is not generally known we will describe it briefly. For fuller details the reader is referred to the original article.⁴

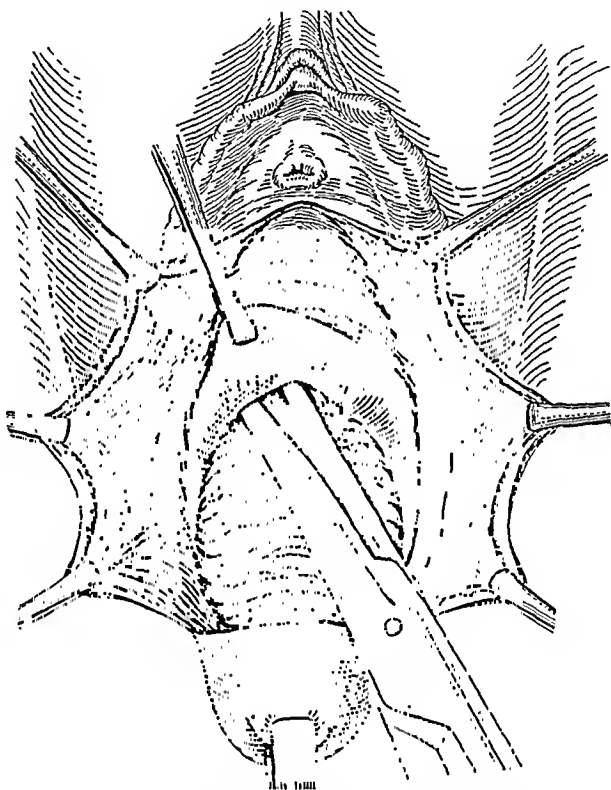


Fig. 1.—The vaginal mucosa has been separated from the bladder, and the bladder is being separated from the cervix.

Technique

(1) The cervix is drawn to the outlet by means of a Jacob's clamp on the anterior lip. A mucosa clip grasps the mucosa about 1 cm. posterior to the urethral meatus. A transverse incision is made through the reflexion of the vaginal mucosa about 1 cm. or two from the external os. With Mayo scissors the anterior vaginal wall is separated from the bladder in the midline by alternately opening and closing the scissors. As each segment of 3 or 4 cm. is separated the vaginal mucosa is cut in the midline, ultimately forming the usual inverted T-shaped incision. (2) The bladder is then separated from its attachment to the cervix by

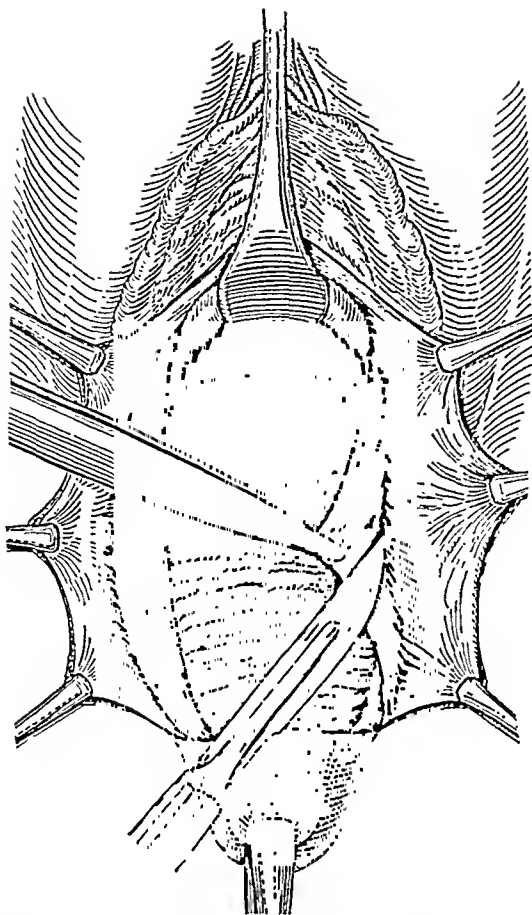


Fig. 2.—Pubovesical fascia is being dissected from vaginal flap. Dotted line indicates line of incision of vesicouterine pouch of peritoneum.

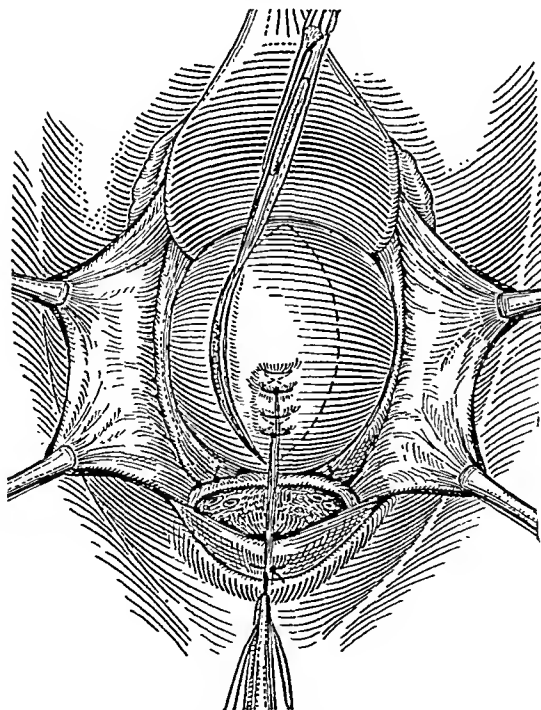


Fig. 3.—Large fundus is being delivered by excising wedge-shaped section. Cervix has been amputated and posterior lip covered over with flap of mucosa.

sharp dissection until the vesicouterine pouch of peritoneum is reached (Fig. 1). (3) The two triangular flaps of vaginal mucosa are held out by assistants and the pubovesical fascia is dissected from each flap (Fig. 2). In the midline this fascia is often thin but laterally it is usually quite sturdy. (4) The cervix is next amputated. Different techniques are permissible for this. We prefer to extend the transverse in-

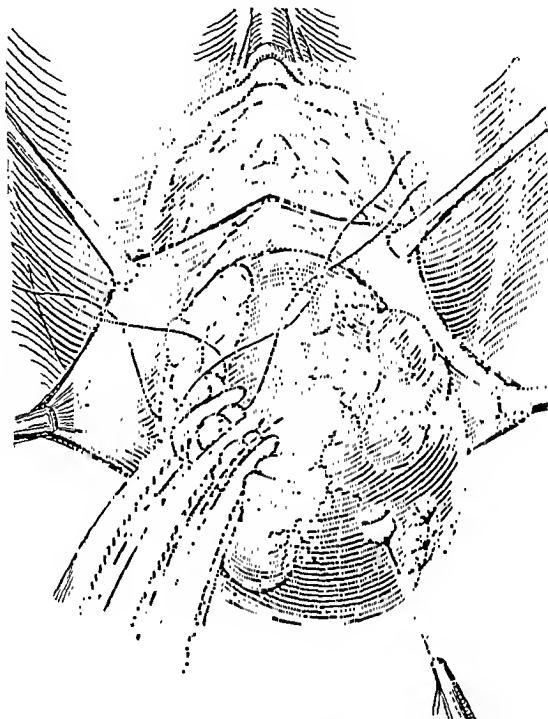


Fig. 4.—Round ligament, tube and ovarian ligament are clamped en masse, cut at the dotted line and doubly ligated.



Fig. 5.—Corpus is being amputated and uterine vessels ligated.

cision mentioned above around the cervix and then dissect a flap of mucosa free posteriorly as in the Sturmdorf operation. The cervical branches of the uterine arteries are ligated bilaterally and the cervix amputated at the desired level. The shortened posterior cervical lip is then covered with the flap of mucosa, using a mattress suture of chromic catgut. (5) The vesicouterine pouch of peritoneum is incised as indicated in the dotted line in Fig. 2 and the fundus delivered. We have

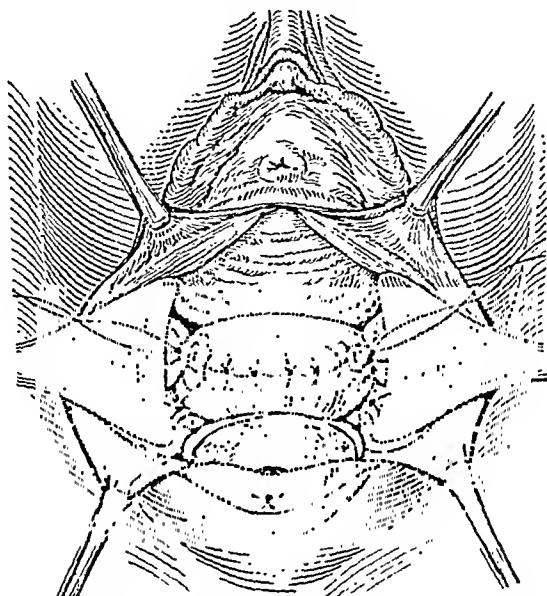


Fig. 6.—Isthmic stump has been closed by interrupted sutures and ligaments and tubes sutured to it.

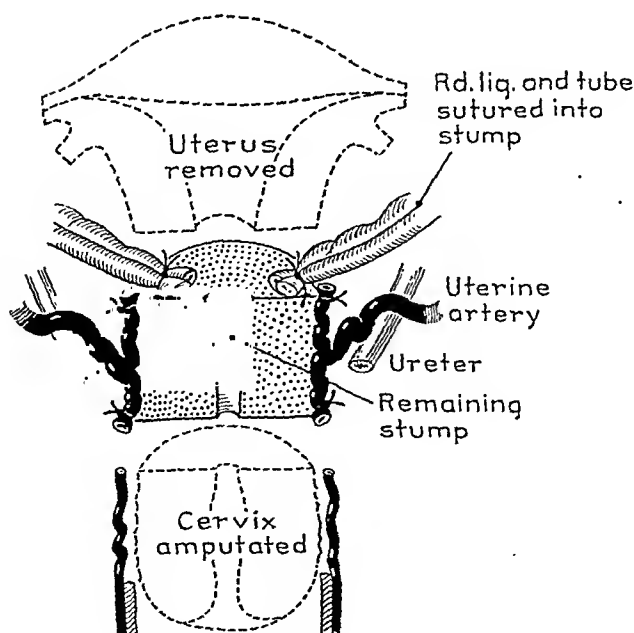


Fig. 7.—Diagram showing isthmic portion of uterus which remains with its intact blood supply. To it have been sutured the round ligaments, tubes and ovarian ligaments (not seen). The bases of the cardinal ligaments and uterosacral ligaments are left attached to the segment.

found traction sutures placed in the corpus very useful for this. If difficulty is encountered in delivering a large fundus completely a wedge-shaped piece of myometrium may be excised as in Fig. 3. (6) The uterine end of the tube, round ligament and ovarian ligament are triply clamped en masse, cut and ligated, as in Fig. 4. This is repeated on the opposite side and a supravaginal hysterectomy done at the desired level (Fig. 5), cupping the stump to permit easier closure. (7) The cervical stump is then closed with interrupted sutures of chromic catgut and the round and ovarian ligaments together with the ends of the tubes are sutured to the angles of the stump (Fig. 6). The segment of the cervix

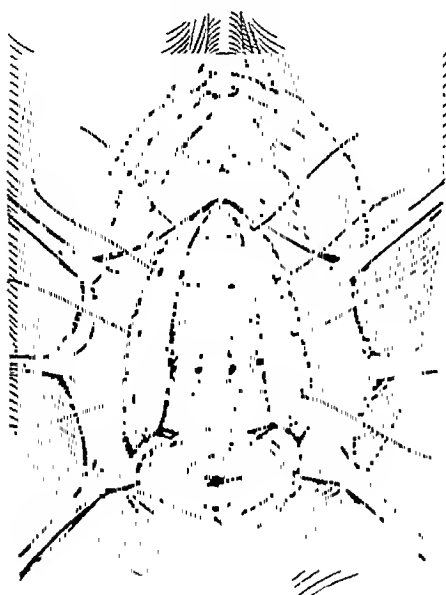


Fig. 8.

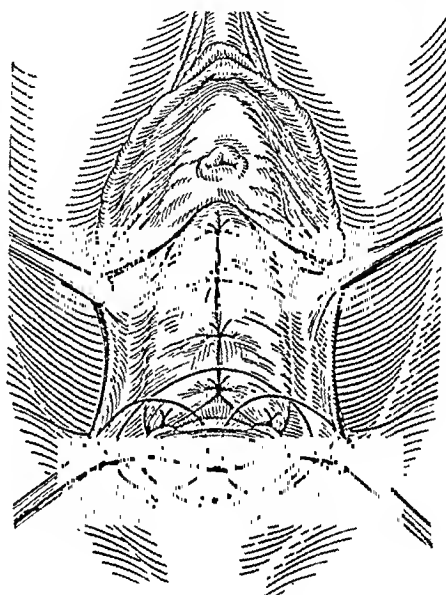


Fig. 9.

Fig. 8.—Sutures have been placed for approximation of pubovesical fascia beneath trigone of bladder and also for attachment of stump to this fascia.

Fig. 9.—Fascia has been completely approximated and mattress suture has been placed for covering the anterior lip with mucosa flaps.

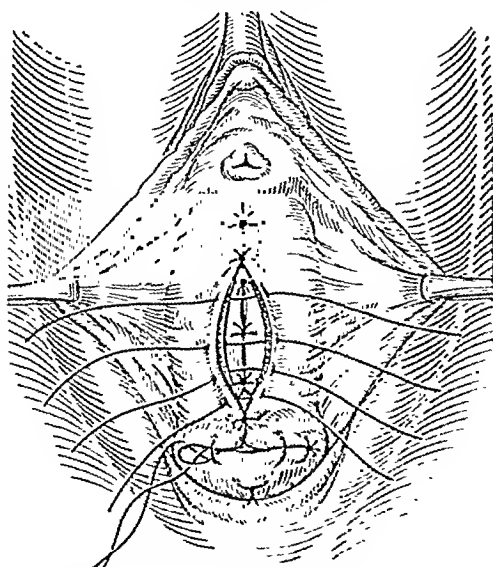


Fig. 10.—Mucosa approximated with interrupted sutures.

which remains attached to the basal portions of the broad ligaments and the uterosacral ligaments is shown in the diagram (Fig. 7). (8) The cut margin of the vesicouterine peritoneum is then sutured to the cervical stump to close the opening in the peritoneum and the stump anchored to the vesicocervical pillars of fascia, thereby bringing it up under the bladder as in the Watkins operation (Fig. 8). The vesicocervical fascia is approximated for its entire length over the stump, the base of the bladder and the urethra (Fig. 9). The excess of vaginal mucosa is then excised and the vaginal incision closed in the midline, the anterior lip of the cervix being covered in the Sturmdorf manner with the divided flap of mucosa (Fig. 10). (9) The pelvic floor and rectocele are then repaired as indicated by the degree of relaxation and the size of the rectocele.

Results

On the private services of E. H. Richardson, Sr., and R. W. Te Linde and on the public ward service at Johns Hopkins Hospital the operation has been performed on approximately 50 women. Some of these have been done too recently to be of value in a follow-up study. We have been able to get back for questioning and examination 33 women who were operated upon from five years to six months ago. There has been no operative mortality. We attribute this in part to our careful selection of cases. It is generally a longer operative procedure than a vaginal hysterectomy and should not be attempted upon frail, elderly women. The average age of our patients was 44 years. The oldest patient was 64 and several more were close to that age. The youngest patient in the series was 27 years. She had had three children and had a second-degree prolapse with a large cystocele. Since she did not desire more children this operation seemed ideal for her and it has proved to be so.

The only postoperative complication of any consequence which we have seen was a broad ligament abscess which formed in a patient operated upon too recently to be included in this series, but the result is good three months after operation. There is the usual difficulty in voiding postoperatively as in any extensive vaginal operation. We have used repeated catheterization in some cases and retention catheters in others. We are not enthusiastic about either of these procedures but know of no better solution. The instillation of one ounce of $\frac{1}{2}$ per cent aqueous mercurchrome in the operating room, which we have used so successfully in our laparotomies in order to induce voiding, has little or no effect in extensive vaginal plastic operations.

In connection with age it is interesting to consider the operation from the standpoint of the preservation of menstruation. The average age of the patients operated upon by Dr. Richardson, Sr., was 55 years and a few of his were premenopausal. However, there has been a tendency to extend the use of the operation to younger women, since one of the advantages of the operation is the use of the interposition principle in younger women without running the risk of subsequently developing myomas, functional bleeding or carcinoma as in the Watkins procedure.

In the group of 18 cases operated upon by Te Linde and by the residents the average age was 35 years. In 10 of the 18 cases, sufficient endometrium was permitted to remain to preserve some menstrual function. We feel that this is psychologically desirable in some young women and an advantage which obviously cannot be offered in vaginal hysterectomy. In all cases except one the menstruation was very scanty, and it was painless in all except two who claimed some menstrual discomfort as before operation.

In the younger women the results as to function of the vagina are important. All of the 23 private cases stated that coitus was painless but 4 of the 10 public ward patients stated that they had slight or occasional dyspareunia. There was no evidence of vaginal constriction in any of these 4 cases and indeed no organic basis for the complaint was found. We are inclined to consider the complaint as evidence of an unhappy marital status so frequently found in the overworked women of the dispensary economic class.

The most important question put to the returned patients was concerning their relief from the symptoms of which they complained before operation. All 23 private patients were completely relieved. Among 10 public ward patients there were 3 who refused to admit complete relief. In two of these there was a perfect anatomic result but in the third there was a moderate cystocele with slight stress incontinence. Among these public ward cases there were, of course, the overworked women with few social advantages, few intellectual resources and multiple complaints. Since the anatomic result was perfect in two of these three women, we feel that it is scarcely justifiable to attribute their incomplete relief to the operation which in all except one instance anatomically corrected the vaginal herniation.

The results of a plastic operation which has for its object the restoration of broken down supports should be considered from an anatomic point of view. Here again it seems desirable to divide the cases into the private group and the public ward cases. Of the 23 private cases the results were anatomically perfect except for a slight recurrent asymptomatic cystocele in one case and a slight urethrocele in another with slight stress incontinence. Among the 10 service cases there was one moderate recurrent cystocele with slight stress incontinence. There was also one case in which the vaginal vault descended slightly but this was entirely asymptomatic.

Discussion

In view of the results of the follow-up of this first series of cases operated upon during the past five years what can be said for or against this operative procedure? It might be advantageous to consider our results by comparing them with the criteria originally laid down by Richardson as the desired objective of any operation for uterine prolapse. The diseased portion of the cervix was removed in all cases and the

absence of discharge from the preserved isthmic portion showed that it did not function as a source of leukorrhea. That portion of the cervix which is most commonly a potential site of carcinoma was removed. The corpus uteri, or the desired portion of it, was removed in each instance, practically eliminating it as a potential site of neoplasm and removing any disease which may have been present at the time of operation. The opportunity was presented at operation to remove the cervical canal mucosa at time of operation, but we rarely felt this necessary and our follow-up has not indicated that it should have been done. There was a minimal destruction of or interference with the blood supply of the units needed to support the vagina. Particularly, the bases of the broad ligaments and uterosacral ligaments were not crushed as in vaginal hysterectomy and hence were better preserved for support of the vagina. All of the normal supporting structures were utilized to effect the complete repair, namely, the pubocervical fascia, the basal portion of the broad ligaments attached to the isthmic portion of the uterus, the uterosacral and round ligaments, the fascia of the rectovaginal septum and the fascia and muscles of the perineum. That these structures have supported the vagina well is shown by the fact that in only one case of the 33 was there a slight descent of the vaginal vault. The two cases of slight recurrent cystocele and one of slight urethrocele could have occurred with vaginal panhysterectomy, for in both operations the approximation of the pubocervical fascia is utilized to cure these conditions. The Watkins operation which utilizes the whole corpus to support the bladder obviously has the advantage in this respect over any of the other procedures used for prolapse. Enterocèles if present were eradicated in this series by dissection of the hernia sac formed by the elongated cul-de-sac, excising it and preventing its recurrence by approximating the uterosacral ligaments in the midline.

That the vagina was restored to its normal depth and caliber is shown by the examination of the organ in the follow-up study and by the report from all of the private patients that coitus was comfortable. In the public ward patients who complained of occasional or slight dyspareunia no anatomic narrowing or shortening of the vagina could be demonstrated. The satisfactory functioning of the vagina has led us to extend the operation to younger women than were originally considered candidates for it by Richardson, provided no further childbearing is considered advisable or is desired by the patient.

Observing that our results have been very satisfactory in this first series of cases operated upon in the past five years, we must admit at the same time that the operation is somewhat more complicated and time consuming than either the vaginal hysterectomy or the Watkins interposition operation. It is not our intention to advocate its routine use in all cases of prolapse. We believe it is contraindicated in elderly, feeble women who are poor operative risks. We have seen the good results ob-

tained in our own clinic with the Watkins procedure and in many women, near or past the menopause, with a large cystocele and a uterus of proper size we believe it is an excellent method of cure. It is a quicker and less shocking operation than either the Richardson composite operation or the vaginal hysterectomy. In many instances, however, it seems desirable to get rid of the corpus uteri for reasons previously mentioned. Then one must choose between the vaginal hysterectomy and the Richardson composite operation. Our results have been better with the latter. In our opinion the chief reason for this is that vital structures upon which the support of the vagina chiefly depends, namely, the strong basilar portion of the broad ligaments and the uterosacral ligaments, have not been crushed and ligated en masse to have their terminal portions slough but have been maintained attached to the isthmic portion of the uterus with their blood supply intact. It is hoped that this report will stimulate others to utilize this operative procedure, for it is only by the general use of any new operation by many surgeons and upon a host of patients that its real value will be finally determined.

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THE UNENGAGED VERTEX IN FULL-TERM PRIMIPARAS*

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THE conduct of labor in a full-term primipara with an unengaged vertex is not generally understood. This conclusion is based on a survey of maternal mortality community records which reveal numerous patients with unengagement that were permitted to labor too long and then were subjected to dangerous operative procedures with severe soft part injury and infection which ended fatally. The seriousness of this problem, therefore, calls for a re-emphasis both in the method of establishing the diagnosis of unengagement and in its management.

Engagement is defined as the mechanism by means of which the presenting part enters the pelvis. When completed, it signifies the passage of the greatest diameter of the fetal head through the superior strait. The most dependent portion of the head should then be felt at or slightly above the level of the ischial spines.

*Read at a meeting of the Section on Obstetrics and Gynecology of the New York Academy of Medicine, November 18, 1942.

In primiparas, engagement of the vertex generally occurs within two weeks of delivery, but it may not take place until active labor sets in. Therefore any primipara with an unengaged head in the last two weeks of gestation should be suspected of having a fetopelvic disproportion and should be carefully observed during the early phases of labor to determine whether or not the presenting part is fixed at the inlet or is entering the pelvis.

At Morrisania City Hospital, unengagement was encountered in 204 cases (10.7 per cent) of 2,149 primiparas (exclusive of twin pregnancy and premature birth) delivered during the period from Jan. 1, 1934, to Dec. 31, 1938. In other words, one of every 10 full-term primiparas was found to have an unengaged presenting part when admitted to the labor room. Of the 204 cases, 183 presented as a vertex, 18 presented as a breech, and 3 were face presentations. Discussion of the breech and face presentations is omitted in this article as they offer entirely different problems compared to the vertex.

Our method of determining engagement or "engageability" is that described by Müller and modified somewhat by Kerr.¹ The patient is placed in the lithotomy position. One hand grasps the fetal head through the abdomen and presses it into the superior strait. Two fingers of the other gloved hand are passed into the vagina to estimate the degree of engagement of the vertex and the size of the pelvic inlet. The thumb of the gloved hand bridges the symphysis pubis and estimates the amount of overriding of the symphysis pubis by the presenting part. Additional pressure may be applied to the fundus of the uterus by an assistant in order to attempt to force the head into the pelvis.

It has been our practice to refer most unengaged primiparas for roentgen pelvimetry to visualize more accurately bony factors which may be responsible for the failure of descent. There is no doubt that an accurate x-ray study of the pelvis early in labor has enabled us time and again to choose more intelligently the procedure best suited in each case.

Following the above routine, our cases fell into one of three categories:

Group A.—The presenting vertex was made to enter the pelvis readily in 45 cases (24.5 per cent). *No true disproportion*, therefore, existed between the head and the pelvis. The failure of early engagement was due generally to (1) a relatively increased amount of amniotic fluid, (2) deflexion, (3) malposition such as occiput posterior or asynclitism, or (4) small baby and justo major pelvis.

All patients in this group were permitted to continue labor without any further regard to the lack of engagement since there was no doubt that they could deliver vaginally. Engagement occurred within twenty-four hours in two-thirds of the cases. In some instances the membranes had to be ruptured artificially at or near full dilatation to permit the vertex to descend.

Thirty-seven patients delivered spontaneously or by prophylactic or low forceps (Table I). Labor was prolonged in 8 other cases due to

TABLE I. GROUP A. NO REAL DISPROPORTION

	NO. CASES	MATERNAL MORTALITY	STILL- BIRTHS	NEONATAL DEATHS
Total	45	0	1	0
Spontaneous delivery	30	0	0	0
Prophylactic forceps	5	0	0	0
Low forceps	2	0	0	0
Midforceps	8	0	1*	0

*Due to intrapartum eclampsia.

transverse arrest or persistence of the occiput in the posterior position in the midpelvis. These women required midforceps extraction. There were no maternal deaths. One baby died during an intrapartum eclamptic convulsion.

The prognosis for this group of primiparas is therefore as good as for primiparas who begin labor with the head definitely engaged.

Group B.—The presenting part could not be made to enter the pelvis because of marked overriding of the symphysis pubis in 16 cases (Table II). *The cephalopelvic disproportion was obvious* and was due to (1) a markedly contracted pelvis, (2) an oversized baby, or (3) hydrocephalus.

TABLE II. GROUP B. OBVIOUS DISPROPORTION

	NO. CASES	MATERNAL MORTALITY	STILL- BIRTHS	NEONATAL DEATHS
Total	16	1	2	1
Cesarean section	14	1*	0	1 (atelectasis)
Spontaneous delivery	1	0	1†	0
Craniotomy	1	0	1†	0

*Maternal death due to sickle cell anemia.

†Both infants were hydrocephalic. The one delivered spontaneously was macerated.

Nine cases were recognized on admission of the patients and all but one patient were immediately delivered by cesarean section. The one exception was that of a primipara who had been in labor for three days before coming to the hospital with a macerated hydrocephalic fetus. The cervix was fully dilated, the membranes were intact, and the fetal heart could not be heard. The membranes were ruptured artificially and within a few hours the macerated fetus was delivered spontaneously.

Six patients were erroneously thought by the junior staff to belong in Group C (see below) and were given a trial of labor, which in three instances lasted from twenty-four to forty-eight hours before the error was discovered. As soon as the correct diagnosis of obvious disproportion was established, however, the low segment cesarean section was done in each instance.

The one remaining case of obvious disproportion was due to hydrocephalus. This patient was admitted in shock following several unsuccessful attempts at high forceps extraction at a private hospital. The cervix was only 3 fingers dilated and the vaginal walls badly lacerated. The shock was treated, and thirty-six hours later when the patient was in better general condition and the cervix fully dilated a craniotomy was done. This woman recovered after a stormy course.

There is little doubt that a competent radiologist would have made the diagnosis and prevented the bungling to which this unfortunate woman was subjected.

There was one maternal death in this group from a postoperative pneumonia in a patient with a sickle cell anemia. One baby delivered by cesarean section died neonatally of pulmonary atelectasis.

Group C.—The degree of overriding of the symphysis pubis was slight or did not exist, but the presenting vertex could not be forced into the pelvis in 122 cases (66 per cent). It was felt that possibly in all these cases the forces of labor could reduce or alter the factors responsible for the cephalopelvic disproportion, and that, given an opportunity, the head would engage in due time and the patient deliver per vaginam. *The disproportion, therefore, could be considered as a relative one.*

The factors which were mainly responsible for the failure of engagement were somewhat similar to those of Group A and consisted of malpositions (occiput posterior and transverse, deflexion attitudes, asynclitism), contracted pelvis, and uterine inertia. Excessive amniotic fluid with intact membranes did not play an important role in this group as in Group A.

All the patients in Group C were given a trial of labor. The trial of labor, as we practice it, begins with the onset of real labor pains (i.e., intermittent uterine contractions accompanied by progressive changes in the cervix). The trial ends when the vertex is definitely engaged or at such time as the staff is convinced that engagement cannot take place, or that further delay will endanger the life of the baby and/or the mother. Consequently our trial of labor is a very flexible one, depending upon individual factors, and lasted from six to forty-eight hours or even longer on occasion.

Group C-1 consisted of 5 patients whose trial of labor lasted up to six hours. All delivered spontaneously or by simple forceps extraction. No x-ray pelvimetry was done because of the fairly rapid descent. There were no occiput posteriors in this group. Two babies were occiput transverse, and one was delivered by low midforceps for maternal exhaustion after a total labor of thirty hours. The reason for unengagement was attributed to intact membranes and a relatively increased amount of amniotic fluid, for the head descended in each instance immediately after the rupture of the membranes. The babies weighed between 7 and 8 pounds. There was no maternal or fetal mortality.

Group C-2 consisted of 41 patients who required six to twelve hours of active labor for engagement to take place. There were 12 occiput posteriors and 7 occiput transverses. Three patients had a true conjugate of less than 10 cm. Twelve babies weighed over 8 pounds. The membranes were intact on admission in 28 cases. As a rule, engagement occurred before full dilatation was reached, regardless of the status of the membranes. In most instances the head was found engaged at about 3 fingers' cervical dilatation.

All delivered spontaneously or by forceps. Since the disproportion was of a severer grade than Group C-1, more frequent forceps extractions were required in midpelvis. There were no maternal or fetal deaths.

One patient in this group embodied some of the difficulties encountered in the management of disproportion and is worth emphasis. This

woman was admitted with irregular pains without any progressive changes in the cervix. The head was unengaged, occiput posterior, and membranes intact. X-ray pelvimetry indicated the true conjugate to be 9.7 cm. and the head floating. The radiologist expressed the opinion that the head would encounter difficulty in passing through the pelvis. Under such circumstances a cesarean section would seem to be the method of choice. Clinically, however, the baby felt small, and in spite of the x-ray prognosis we decided to see what would happen when the patient went into real labor. After two days of preliminary ineffectual pains, active labor set in and within eight hours the vertex entered the pelvis and shortly thereafter the patient delivered a 5½ pound baby.

Group C-3 consisted of 24 patients who exhibited engagement after twelve to eighteen hours of trial labor. These included 8 occiput posteriors, 5 occiput transverses, 2 contracted pelvis (x-ray confirmation), and 6 large babies. The membranes were intact in 20 instances. Here again engagement took place after the cervix dilated to 2 or more fingers regardless of the status of the membranes.

Thirteen of the women delivered spontaneously. One mother and one baby died. The maternal death was interpreted at autopsy to have resulted from a spontaneous rupture of a pyosalpinx during labor, causing a generalized peritonitis. The fetal death occurred neonatally due to adrenal hemorrhage and pulmonary edema.

Eleven patients required forceps assistance. There were an increased number of midforceps applications due to arrested posterior and transverse positions. Two babies died of intracranial injury resulting from forceps trauma. One maternal death followed a low midforceps delivery in which there were soft part laceration and excessive bleeding. The patient died of anuria on the third day post partum following a transfusion accident.

In two other patients, no engagement resulted after ten to fourteen hours of trial labor, respectively, and the patients were delivered by cesarean section. No particular reason could be ascribed to this choice of delivery at this time except that the attending obstetrician elected to discontinue the trial. The babies were of average size and the pelvis slightly contracted. In neither case was the cervix fully dilated at the time of operation. One woman, with ruptured membranes on admission, was delivered through a low segment uterine incision. She recovered. The other patient, with intact membranes, was delivered through a low classical incision and died of peritonitis.

Group C-4 consisted of 18 primiparas who did not show engagement until labor had been in progress for eighteen to twenty-four hours. Eleven patients had an occiput posterior, and 3 had an occiput transverse. Two babies weighed over 8 pounds. Four patients had a contracted pelvis. The membranes were intact on admission in 14 instances. Engagement occurred when the cervix was more than 2 fingers and less than 5 fingers dilated whether the membranes were intact or ruptured.

Seven patients delivered spontaneously. Eleven others required forceps assistance. There were no maternal or fetal deaths in this group.

One other patient failed to engage after a twenty-four-hour trial of labor and was subjected to a cesarean section. On admission the pains were not very strong, the cervix admitted the tip of 1 finger, the membranes were intact, the pelvis was borderline, the baby was of average size and in the occiput posterior position. The membranes ruptured

spontaneously after seven hours of labor. At the end of twenty-four hours, the cervix was only $2\frac{1}{2}$ fingers dilated, the head was still unengaged, and the vaginal discharge had become foul-smelling. The attending obstetrician felt an adequate trial of labor had been given this woman and terminated labor by a peritoneal exclusion type of operation with drainage. A living $6\frac{1}{2}$ pound baby was delivered. Convalescence was complicated by a severe wound infection.

Group C-5 consisted of 24 primiparas who engaged after a trial of labor lasting from twenty-four to forty-eight hours. There were 12 occiput posteriors and 6 occiput transverses. X-ray pelvimetry was done in 12 instances, and 3 were found to have a contracted pelvis. There were 6 large babies. The membranes were intact on admission in 20 instances. Except in one case to be described later, engagement occurred when the cervix was 2 to 4 fingers dilated, regardless of the status of the membranes.

Four patients delivered spontaneously. Nineteen were assisted by forceps, most of which took place at higher pelvic levels than in the preceding groups. One patient sustained a prolapse of the cord when the membranes ruptured spontaneously with the cervix $4\frac{1}{2}$ fingers dilated. A version and breech extraction was done but the baby was born dead.

The high incidence of operative interference in this group was the result of more marked fetopelvic disproportion with arrest of the vertex in the midpelvis, secondary uterine inertia, fetal distress, and maternal exhaustion.

There was one maternal death which occurred in a 30-year-old primipara who was admitted after twelve hours of labor pains and with intact membranes. The head was floating, L.O.A., and the cervix was $1\frac{1}{2}$ fingers dilated. X-ray pelvimetry disclosed the true conjugate to be 10.0 cm. The membranes ruptured spontaneously after twenty-eight hours of labor, at which time the cervix was 3 fingers dilated and the vertex still unengaged. The fetal heart disappeared at the thirty-sixth hour of labor. The head was believed to be engaged at the forty-eighth hour of labor with the cervix not yet fully dilated. In the meantime the temperature rose to 103° F. due to an intrauterine infection. Fluids were administered intravenously. The first stage ended after sixty-three hours of labor with the vertex just about engaged within the inlet. A high midforceps was then performed and a dead baby extracted. The placenta delivered spontaneously. The patient died ten days post partum due to a gangrenous uterus and peritonitis.

We quote this case as an example of the consequences of mismanagement.

Four babies died in the interval between engagement and delivery. The cause of death was ascribed to the prolonged and protracted labor. Four other babies died of trauma resulting from difficult forceps extraction. Another baby died following a prolapse of the cord (mentioned previously). The fetal mortality for this group was 41.6 per cent.

Four other patients failed to engage after a twenty-four- to forty-eight-hour trial of labor and were delivered by a low segment cesarean section. All these mothers and babies were discharged well.

Group C-6 consisted of two primiparas in whom engagement occurred after a trial of labor that extended from forty-eight to seventy-two hours. Both had occiput posteriors and contracted pelvises. The membranes ruptured spontaneously before admission or shortly thereafter. Engagement took place at full dilatation. One patient was delivered by

high midforceps for fetal distress after a second stage of one and one-half hours and the baby died of instrumental trauma. The weight of this baby is not recorded. The other patient was successfully delivered of a 7½ pound baby by low midforceps.

In another primipara engagement failed after a first stage labor of forty-nine hours with ruptured membranes, and she was delivered by a low segment cesarean section without maternal or fetal mortality.

Comment

It is not the intention of the authors to imply that every primipara with the vertex unengaged can be correctly classified at the first examination. The factors responsible for unengagement are so varied that trained obstetricians experience difficulty. Consequently, if a patient fails to make the expected progress, a re-evaluation of the facts becomes necessary to determine whether the original impression was correct. Thus, a case of obvious disproportion may be treated as one of relative disproportion for as much as twenty-four hours. Reconsideration should establish the true state of affairs before meddling interference with forceps and/or version makes cesarean section a dangerous procedure.

The safest attitude to assume when confronted with an unengaged vertex presentation in a primipara is that a cephalopelvic disproportion exists. The patient should be considered as a potential candidate for a cesarean section and guarded accordingly.

If obvious disproportion exists, a cesarean section is indicated without further delay unless the fetus is dead or abnormal.

If an obvious disproportion is excluded, the patient may then be permitted to continue in labor. Since the average primipara dilates fully within twenty-four hours, it is reasonable to expect that engagement will occur in this interval. This actually happened in 50 per cent of our patients with cephalopelvic disproportion of the apparent or relative type.

The prognosis for patients with no true disproportion is exceedingly good even though labor may be somewhat prolonged.

The prognosis for patients with relative cephalopelvic disproportion who engage in less than twenty-four hours of labor is as good as in a comparable group of cases that are engaged at the onset of labor. On the other hand, if engagement fails to take place within this interval, and the trial of labor is continued, the fetal mortality rate will rise precipitously due to the protracted labor, to difficult forceps applications, and to intrauterine infection. Our fetal mortality for such cases was 41.6 per cent.

This tremendous loss of babies raises the issue as to whether these primiparas should be permitted to have a trial of labor of over twenty-four hours.

The argument is advanced that these same women will probably deliver vaginally without much difficulty in succeeding pregnancies, mak-

ing the possible sacrifice of the first born more desirable than subjecting them to a cesarean section at the end of each pregnancy. It is difficult to evaluate the truth of this argument, for there are no available statistics on the subject. While obstetricians may have experienced cases of this type, it is not usual for a disappointed primipara to return to the same obstetrician in succeeding pregnancies. Furthermore many of these women remain sterile due to the trauma and infection common to prolonged and instrumental deliveries.

Abdominal cesarean section will prevent this excessive loss of babies, but increases the risk to the mother. This risk is a very considerable one if the classical type of operation is performed routinely. Consequently, the adherents of the classical cesarean section teach that the trial of labor be restricted to less than twelve hours, especially when the membranes are ruptured, or else there will result a high maternal mortality due to peritonitis.² Possibly the intraperitoneal use of sulfanilamide may reduce the incidence of peritonitis to a level where the classical type of operation may be resorted to with greater safety.

At the present time, if the low segment (two flap) operation or other completely extraperitoneal operation is performed after twenty-four hours of trial labor, the maternal mortality will not be much higher than that of vaginal delivery. Cosgrove³ states that the maternal risk is not increased, even if thirty-six hours have elapsed, provided that the Water's type operation is done. The justification for this attitude is seen in the increasing number of women who will deliver vaginally if cesarean section is deferred. Had we been less conservative, our incidence of cesarean section for relative cephalopelvic disproportion would have increased at least 200 per cent.

The onset of active labor is not always readily determined. Many patients will have "false" or "preliminary" pains for several hours, even days, without any detectable alteration in the cervix, except possibly that of retraction. Eventually the more progressive type of labor pains set in. The onset of the trial of labor should be calculated from the time this change in the character of the labor pains occurs. If, however, true primary uterine inertia exists, it is best to do an early cesarean section, particularly if the patient is of the dystocia dystrophy type.

Attempts to shorten the first stage by accouchement forcé, Dührssen's incisions of the cervix, and bagging, hasten cervical dilatation but do not eliminate the cephalic and pelvic factors responsible for the disproportion. These traumatic maneuvers have no place in the management of a case undergoing a trial of labor. We have on a few occasions resorted to Dührssen's incisions of the cervix but only after engagement had taken place.

Intact membranes may prevent engagement when no true disproportion exists (Group A), and artificial rupture of the membranes may be safely practiced early in the first stage to encourage descent of the head. It is likewise safe to do this in cases of relative cephalopelvic

disproportion if the cervix dilates fully in less than six hours (Group C-1). When confronted with the other groups of relative cephalopelvic disproportion, it is best to keep the membranes intact until the cervix is fully dilated or nearly fully dilated, because the failure of engagement is not the result of the buoyancy influence of the amniotic fluid. Early artificial rupture of the membranes in these patients frequently causes pressure edema of the cervix which delays further dilatation, prolongs labor, and creates maternal exhaustion.

In all cases of prolonged labor it is common practice to use sedation to avoid maternal exhaustion. When morphine was prescribed for patients undergoing a trial of labor, occasionally a temporary cessation of labor resulted. When the effects of the morphine wore off, the pains were not always as strong nor as effectual as before the drug was given. This was not observed after the use of barbiturates. It would appear, therefore, to be more preferable not to order morphine until after engagement has been completed.

The management of relative cephalopelvic disproportion when complicated by organic heart disease, placenta previa, premature separation of the placenta, or toxemia of pregnancy must be modified to comply with the associated disease. It is questionable whether any trial of labor ought to be given under such circumstances.

Elderly primiparas (over 35 years of age) and patients with a long-standing history of sterility should have a short trial of labor because of the importance of obtaining a living child, particularly if the membranes rupture before the onset of labor, or if the labor pains are irregular and ineffectual. On the other hand, if labor is active and progressive and engagement is not delayed, these patients may be permitted to deliver vaginally even though forceps assistance may be necessary.

Can the problem of fetopelvic disproportion be avoided by inducing labor prematurely? We have had no such experience. Peel⁴ analyzed 100 consecutive cases of surgical induction of labor for real or suspected disproportion among primiparas. The stillbirth rate was 20.8 per cent and the forceps rate was 35.8 per cent. Evidently this so-called prophylactic treatment of disproportion raises obstetric problems more difficult and dangerous to solve than the one it is supposed to correct.

Conclusion

The management of a primipara with an unengaged vertex calls for a display of keen diagnostic acumen and technical skill. The average physician has not had adequate experience to conduct such cases properly. Therefore consultation should be sought for and obtained either before the onset of labor or during the first twelve hours of labor. Each patient can then be correctly grouped and treated accordingly.

In the presence of relative cephalopelvic disproportion, a trial of labor may be given. The duration of the trial must be governed by the patient's progress, the obstetrician's skill with operative measures, and

the environment (hospital or home). Our experience at Morrisania City Hospital indicates that the trial of labor should not exceed twenty-four hours unless there is little hope of obtaining a live and healthy baby, or cesarean section is contraindicated. By adhering to this plan, the fetal mortality will be greatly reduced without adversely affecting the maternal outcome.

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THE HISTOLOGIC APPEARANCE OF THE ENDOMETRIUM DURING LACTATION AMENORRHEA AND ITS RELATIONSHIP TO OVARIAN FUNCTION*

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IT IS a common observation that during the amenorrheic phase of lactation, conception occurs with relative infrequency. This clinical fact has led to the belief that during lactation amenorrhea, as in other types of amenorrhea, the ovulatory phenomenon is held in abeyance. The fact that some women do conceive during this period has brought up the question of the degree of suppression of ovarian activity. Is ovulation completely inhibited, and if so, what is the probable explanation of this inhibition? With this question the present study is directly concerned.

Of the numerous methods used to determine the presence of ovulation in women the one which has received most universal application is the histologic study of endometrial biopsy specimens. It has been generally conceded that formation of a progestational endometrial pattern is conclusive evidence that ovulation has taken place. Similarly, the absence of progestational changes implies that ovulation has not occurred, although it does not prove it.¹ Failure of ovulation cannot be definitely established as a fact without microscopic study of the ovaries,² unless it is assumed that ovulation is invariably followed by luteinization, which may not always happen,³ and that luteinization always produces a secretory endometrium. This last supposition has not been confirmed by studies of pregnanediol.⁴⁻⁶ Nevertheless, the role of endometrial biopsy in excluding the occurrence of ovulation has been well summarized by

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Rock.⁷ "If biopsies, repeated at perhaps weekly intervals, all reveal proliferating endometrium, one may say that ovulation is absent, and that the ovaries give rise to a succession of follicles which function for a time and then regress without rupture." In this investigation an attempt was made to approach as closely as possible fulfillment of this requisite.

Very little work has been done in the study of endometrial biopsies during the period of lactation. Kurzrok, Lass, and Smelser⁸ took premenstrual endometrial specimens from regularly menstruating lactating women. Of a total of 194 biopsies, they found that only 45 per cent showed secretory changes. Griffith and McBride⁹ obtained biopsy specimens from 21 normal lactating women at intervals of three to twenty-four weeks post partum and found that only one woman ovulated prior to the resumption of menstruation. This present investigation is confined to the period of lactation amenorrhea, biopsies having been taken from as early as six weeks to as late as thirty-one weeks post partum. Only one specimen was taken prior to the sixth week and this was done, inadvertently, at the fourth week. To invade the uterine cavity sooner than six weeks post partum was regarded as inadvisable because of the risk of infection. It has been shown that although regeneration of the endometrium outside of the placental site is completed by the end of the third week post partum, the placental site itself does not entirely disappear until the end of the seventh week.¹⁰

Procedure

All biopsies were taken in the out-patient department, with a very small, sharp curette, longer, but no wider than a No. 1 Sims' curette. This instrument was found to be preferable to the suction curettes commonly used, not only because the sharp curette induced less pain, but also because it yielded better specimens of endometrium. An attempt was made to procure one representative strip of endometrium, from the fundus to just above the level of the internal os. Only in cases of hypoplasia was more than one stroke of the curette necessary. No anesthetic was used. Antisepsis consisted in the application of iodine to the outside and inside of the cervix. No case of infection occurred. From each woman included in this study, at least four acceptable biopsy specimens were obtained; those women from whom three or fewer specimens were obtained were excluded. Thus, 145 biopsies, taken from 28 women, were suitable for study. The patients varied in age from 18 to 38 years, the majority being in their twenties. There were 8 Negroes and 20 white women. All were gynecologically normal and had had regular menstrual cycles. Biopsies were taken as often as possible, sometimes as often as every week, as is shown in Table I.

Results

Of the 145 specimens, 136 (94 per cent) were estrogenic; 9 (6 per cent) were progestational. All the progestational endometria were associated with the onset of the first menstrual flow, as shown in Table II. In Case 19 the flow began four hours before the biopsy was done.

TABLE I. RESULTS OF 145 ENDOMETRIAL BIOPSIES

CASE	AGE	COLOR	PARITY	NO. OF BIOPSIES	WEEKS POST PARTUM WHEN BIOPSY WAS TAKEN	ESTROGENIC	PROGESTATIONAL
1	21	B	ii	4	6-8-10-14	4	0
2	24	B	ii	4	9-13-15-21	4	0
3	24	W	i	4	12-14-16-20	3	1
4	27	W	i	5	10-12-16-18-20	5	0
5	25	W	i	4	6-9-12-15	4	0
6	18	W	i	4	10-16-19-23	4	0
7	25	B	i	4	6-9-11-13	4	0
8	27	W	ii	7	6-7-9-12-17-20-28	7	0
9	22	B	i	5	7-8-10-12-15	4	1
10	32	W	ii	5	7-8-10-13-24	4	1
11	38	B	vi	7	10-15-18-22-26-30-31	7	0
12	26	W	iv	9	8-9-11-14-17-20-23-26-29	9	0
13	20	B	i	6	7-8-10-12-16-18	5	1
14	26	W	ii	4	8-11-18-28	4	0
15	25	W	iii	5	7-8-10-12-15	4	1
16	38	W	vii	8	6-8-9-12-15-19-23-26	8	0
17	21	B	i	5	6-8-10-13-17	4	1
18	27	W	ii	8	5-6-8-10-16-20-21-22	8	0
19	19	B	i	6	7-8-9-11-13-16	5	1
20	24	W	ii	6	7-8-9-11-14-17	5	1
21	33	B	v	5	8-9-10-13-16	5	0
22	36	W	ii	5	7-8-9-11-13	5	0
23	33	W	vii	5	6-7-8-11-14	5	0
24	22	W	i	4	8-9-10-12	4	0
25	19	W	i	4	8-9-10-11	3	1
26	31	W	iv	4	4-5-6-7	4	0
27	24	W	i	4	6-7-8-9	4	0
28	32	W	iii	4	6-7-8-9	4	0
				145		136	9

TABLE II. TIME RELATIONSHIP BETWEEN THE SECRETORY ENDOMETRIUMS AND ONSET OF MENSTRUATION

CASE	ENDOMETRIUM	ONSET OF FIRST MENSTRUAL FLOW
3	Early progestational	2 days after biopsy
9	Late progestational	1 day after biopsy
10	Late progestational	3 days after biopsy
13	Early progestational	10 days after biopsy
15	Mid progestational	5 days after biopsy
17	Late progestational	1 day after biopsy
19	Late progestational	4 hours prior to biopsy
20	Late progestational	7 days after biopsy
25	Early progestational	4 days after biopsy

The endometrium of this patient is demonstrated in Fig. 1. In Case 13 the first period began ten days after the specimen (Fig. 2) was taken. In the 7 other cases the flow began in from one to seven days after biopsy.

Of the 136 estrogenic endometriums, 20 (15 per cent) were very poorly developed and were difficult to obtain. Most of them showed only distorted epithelial fragments, a small amount of stroma, with few, if any, small glands. These poorly developed estrogenic specimens have been classified by various investigators as "hypoplastic,"^{7, 11} "atrophic,"¹²⁻¹⁴ and "hypoestrogenic."¹¹ A typical specimen is reproduced in Fig. 3. Occasionally, however, an intact specimen of endometrium, together with some myometrium, showed very poor estrogenic stimulation, and closely resembled a typical postmenopausal section of endometrium. In



Fig. 1.



Fig. 2.

Fig. 1.—Case 19. Late progestational endometrium, taken four hours after the onset of the first menstrual period. A large part of the tissue is devitalized. ($\times 100$.)

Fig. 2.—Case 13. Early progestational endometrium, taken ten days prior to the first menstrual period. ($\times 100$.)



Fig. 3.



Fig. 4.

Fig. 3.—Case 18. Hypoplastic endometrium, taken ten weeks post partum. This picture prevailed until the twenty-second week, when a proliferative endometrium was obtained. ($\times 100$.)

Fig. 4.—Case 16. Atrophic endometrium, taken six weeks post partum. The endometrium is very thin, the stroma dense and compact, containing only a few small glands just above the myometrium. ($\times 100$.)

these the stroma was fairly dense, showing very few small glands, and the entire endometrium was very thin. This is shown in Fig. 4. The poorly developed estrogenic endometrium occurred in only 8 out of the 28 women studied. Of the 20 specimens, 14 occurred in 4 women and 6 in the other 4 women, as is shown in Table III. They appeared at various times during the amenorrhea, sometimes at the beginning, at other times toward the end, but most often in the middle. In all cases their occurrence was only temporary.

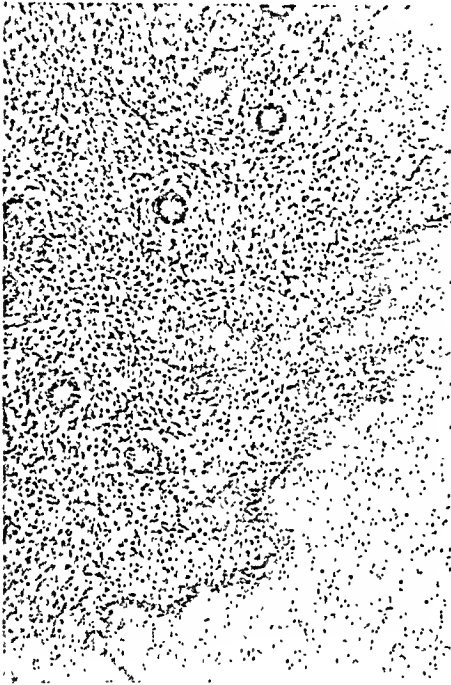


Fig. 5.

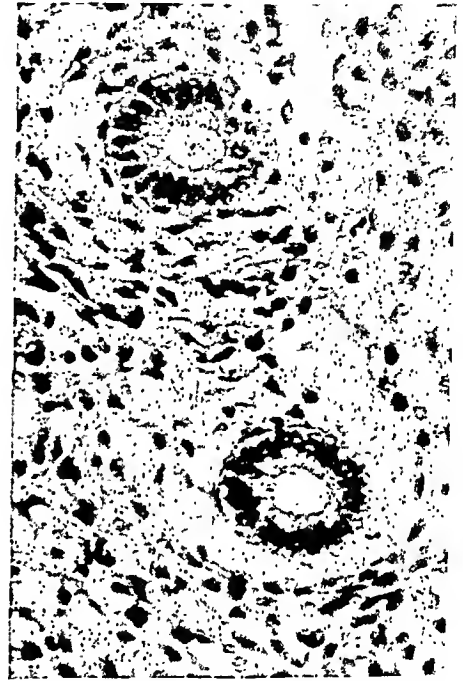


Fig. 6.

Fig. 5.—Case 6. Early proliferative endometrium, taken ten weeks post partum. This picture is identical to that seen at about the end of the first week of the normal menstrual cycle. ($\times 100$.)

Fig. 6.—Case 6. Early proliferative endometrium, showing the loose, avascular stroma with spindle-shaped cells, the columnar glandular epithelium with large dark nuclei. ($\times 400$.)

TABLE III. DISTRIBUTION AND DURATION OF THE 20 SPECIMENS OF ENDOMETRIAL HYPOPLASIA

CASE	NO. OF HYPO- PLASTIC ENDO- METRIUMS	WEEKS POST PARTUM	NO. OF PROLIFERATIVE ENDOMETRIUMS	WEEKS POST PARTUM
11	3	18-22-26	4	10-15-30-31
12	3	14-17-20	6	8-9-11-23-26-29
15	1	10	3	7-8-12
16	4	8-9-12-15	4	6-19-23-26
18	5	8-10-16-20-21	4	5-6-21-22
20	2	7-8	3	9-11-14
21	1	8	4	9-10-13-16
22	1	13	4	7-8-9-11

Of the 136 estrogenic endometriums, 116 (85 per cent) were fairly well developed, presenting all the characteristics of the midfollicular phase of development, as is seen at the end of the first week of the



Fig. 7.



Fig. 8.

Fig. 7.—Early proliferative endometrium, taken from a normal, regularly menstruating, fertile woman two days after cessation of flow. ($\times 100$.)

Fig. 8.—Late proliferative endometrium, taken from the same patient twelve days after cessation of flow, three days after regularly occurring "mittelschmerz." ($\times 100$.)

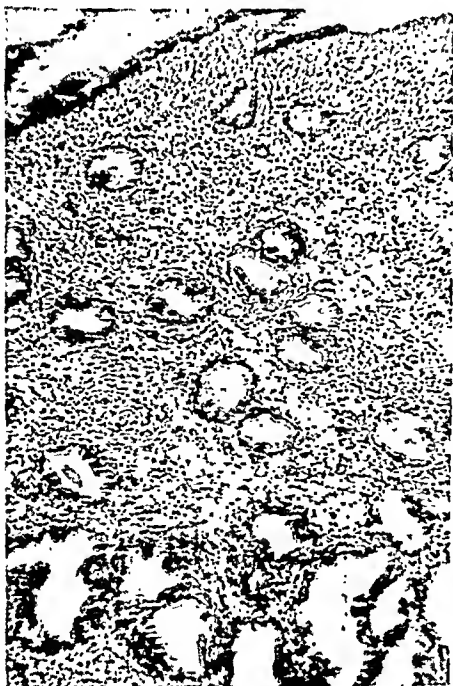


Fig. 9.



Fig. 10.

Fig. 9.—Late secretory endometrium, taken from the same patient three days prior to flow. Compare the cyclic changes in Figs. 7, 8, and 9 to the static pictures of Figs. 10, 11, 12, and 13. ($\times 100$.)

Fig. 10.—Case 27. Early proliferative endometrium, taken six weeks post partum during lactation amenorrhoea. Compare with Fig. 7, with which it is identical in appearance. ($\times 100$.)

menstrual cycle. A representative specimen is shown in Figs. 5 and 6, taken ten weeks post partum. The glands were always simple tubular, usually round on section, relatively small and undilated. They were generally, but not invariably, constant in size, and most often fairly widely separated. In most instances, with low magnification (X100), about 10 to 12 glands per field were present, but sometimes twice as many. The glands were lined by moderately high columnar epithelium containing relatively large dark-staining nuclei located at varying levels

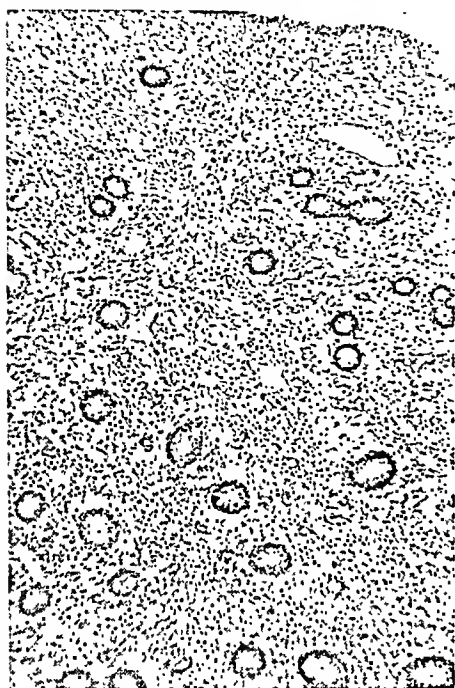


Fig. 11.



Fig. 12.

Fig. 11.—Case 27. Early proliferative endometrium, taken seven weeks post partum. Identical in appearance to Fig. 10. (X100.)

Fig. 12.—Case 27. Early proliferative endometrium, taken eight weeks post partum. Compare with Figs. 10 and 11. (X100.)

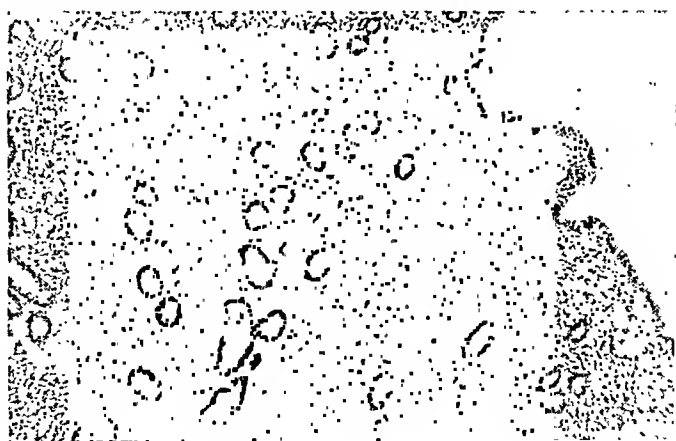


Fig. 13.—Case 27. Early proliferative endometrium, taken nine weeks post partum. These last 4 figures demonstrate the static nature of the endometrium during lactation amenorrhea. (X100.)

of the cells, giving at times the so-called "piled-up" appearance. The nuclei, as a rule, occupied about one-half of the cell. The stroma was usually very loose and relatively avascular. The stromal cells were mainly spindle-shaped with scanty cytoplasm and, very often, elongated nuclei. This endometrial phase has been classified as "regular estrin,"¹⁵ "early proliferative,"^{16, 17} "early follicular,"¹² "follicular,"¹⁸ and "normal estrogenic."¹¹ This picture was constant throughout the period of amenorrhea, and except for the instances of hypoplasia, showed no variance. The cyclic endometrial changes of a normal, fertile, regularly menstruating woman are shown in Figs. 7, 8, and 9, and, in contrast, the static nature of the endometrium of lactation amenorrhea is shown in Figs. 10, 11, 12, and 13, taken at weekly intervals. The persistence of this picture, therefore, would place it in Herrell and Broders'¹⁹ "persistent early proliferative phase" or in Hamblen's¹⁵ "phase of irregular estrin action."

Discussion

The Endometrium and Ovarian Function.—Herrell¹⁶ has stated, "The ovary, unlike most endocrine glands, has a mirror in which it reflects its activity. This mirror of ovarian activity is the endometrium." During lactation amenorrhea, according to this study, the endometrium is in a state of "undifferentiation." Ovulation, therefore, is probably absent. Furthermore, the endometrium is usually (85 per cent) in a state of "early undifferentiation," as is seen during the first week of the normal menstrual cycle. This suggests that the ovarian follicle is not fully developed. The identical appearance of serial biopsy specimens, many of which were taken at weekly intervals, implies that the follicle is neither maturing nor regressing, that the ovarian cyclic changes have been replaced by a condition of "follicle stasis." However, the occurrence of endometrial hypoplasia in 15 per cent of the specimens shows that follicle regression may take place. The fact that the state of hypoplasia is only temporary implies that following involution of one follicle, another has begun to develop. That a typical hypoplastic endometrium, as has been found here, may be merely a temporary phenomenon, has an important clinical implication. Herrell and Broders,¹⁹ for instance, claim that such an endometrium is indicative of a bad prognosis, regardless of the type or duration of therapy. This statement is true only because of the ineffectiveness of our present therapeutic endocrine preparations, not because of the inherent impossibility of restoring normal ovarian function.

The endometrial findings in lactation amenorrhea differ in no way from those in amenorrhea caused by endocrine imbalance. Thus, according to Rock, Bartlett, and Matson,²⁰ out of 77 biopsies taken from 54 amenorrheic women there were only 8 secretory endometria, the others being either proliferative or hypoplastic. They say that "ovulation infrequently occurs in patients who are habitually amenorrheic." Kotz and Parker¹² have stated that "in amenorrhea the endometrium is usually in a state of follicular arrest or atrophy—no luteal phase is present." Rock and Bartlett¹¹ have claimed that "the estrogenic phase of endometrial development may persist almost indefinitely without menstruation," and found that 5 out of 16 proliferative endometrial specimens were taken more than one year after the last menstrual period. These authors believe that from all endometria where secretory changes have appeared, menstrual flow will invariably occur. Of over

300 secretory biopsy specimens they found only two cases which were not followed within sixteen days by menstrual flow, and in one of these menstruation occurred twenty days after biopsy.

These findings are in accord with those of this study, in which the occurrence of a progestational endometrial pattern was invariably associated with the onset of the first menstrual period.

Thus, study of endometrial patterns during lactation amenorrhea demonstrates that in the amenorrheic state there is inhibition of ovarian activity, the follicles failing to mature to the point of rupture.

Lactation and Ovarian Inhibition.—The anterior lobe of the pituitary gland elaborates a hormone, prolactin, extracted from the urine of lactating women,²¹ which has been shown to be galactogenic in guinea pigs, rabbits²² and monkeys,²³ but not definitely in human beings (note the conflicting reports of Stewart and Pratt²⁴ and Kenny and King²⁵). Prolactin, moreover, has been found to possess definite inhibiting power on gonadal function in lower animals. Inhibition of the estrus cycle in rodents with the use of prolactin has been clearly demonstrated.²⁶⁻²⁸ That this antigonadal action is by way of inhibition of the hypophysis has been demonstrated by Bates, Riddle, and Lahr.²⁹ They have shown that when used alone prolactin induces gonadal atrophy in adult pigeons. However, when used simultaneously with the pituitary follicle-stimulating hormone, prolactin produces gonadal atrophy only when the concentration of follicle-stimulating hormone falls below the level necessary to maintain gonadal action.

Other investigators^{30, 31} have shown that the estrus-inhibiting action of prolactin is due to contamination with the luteinizing hormone (also found in the urine of lactating women). They claim that the luteinizing hormone, or some similar substance, is responsible for lactation amenorrhea in women, and suggest the possibility of its use in the treatment of dysfunctional uterine bleeding. If true, the estrus-inhibiting effect of luteinizing hormone must be directly on the genital tract, rather than through the intermediary corpus luteum. This is proved by the fact that destruction of the corpora lutea in lactating rats does not interfere with diestrus,³² and by the failure of administered progesterone to affect the estrus cycle of rats.²⁸ Furthermore, it is reasonable to assume that if the luteinizing hormone were responsible for lactation amenorrhea ovulation would be present, which is not the case.

Whether the lactating mammary gland itself produces an internal secretion which inhibits ovarian activity has not been conclusively established. The experiments of Cherry³³ have shown that the ovarian cycle can be inhibited by the use of extracts of lactating mammary gland. He has noticed absence of corpora hemorrhagica and corpora lutea in rabbits and albino rats following administration of these extracts. That lactating mammary gland extract, like prolactin, inhibits ovarian activity by suppressing the gonadotropic activity of the anterior pituitary gland has also been proved by that investigator. He has found that administration of gonadotropic substance, in the form of placental extract, produces corpora hemorrhagica and lutea in the experimental animals. When combined with lactating mammary gland extract, however, gonadotropic substance produces neither corpora lutea nor corpora hemorrhagica. Cherry treated 50 women having dysfunctional uterine bleeding

with this lactating mammary gland extract and found that practically all the patients improved. One patient, who was overtreated, developed amenorrhea.

It must be borne in mind that the action of both prolactin and lactating mammary gland extract on the ovarian cycle in the human being has not been proved as yet. That the human ovarian cycle is inhibited by the phenomenon of lactation must be inferred not only by the results of animal experimentation, but also by the clinical evidence derived from endometrial study. No reliable statistics are at present available in regard to the frequency of ovulation in normal, regularly menstruating, fertile women. Rock, Bartlett, and Matson²⁰ have shown that in a study of 392 women of low fertility only 9.1 per cent had anovulatory menstruation. Kurzrok, Lass, and Smelser⁸ have shown that of 47 regularly menstruating, lactating women, 55 per cent had anovulatory flow. This investigation has shown that in the amenorrheic period of lactation ovulation does not occur. Therefore, the lactation phenomenon is in some way responsible for the suppression of ovarian function. The experiments mentioned above seem to show that this suppression is due to inhibition of the gonadotropic activity of the hypophysis, by prolactin or by some hormone elaborated by the lactating mammary gland itself.

Summary

1. A total of 145 endometrial biopsies was done on 28 normal lactating women during the period of lactation amenorrhea.
2. Of the 145 specimens, 9 (6 per cent) showed progestational changes, and all these were associated with the onset of the first menstrual flow.
3. There were 136 specimens (94 per cent) which showed estrogenic changes, and of these, 20 (15 per cent) were hypoplastic.
4. The relationship between the endometrial findings and ovarian function is discussed.
5. The relationship between lactation and ovarian function is considered.

Conclusions

1. The endometrium during the period of lactation amenorrhea is similar to that found in amenorrhea caused by other factors; it shows diminished estrogenic stimulation.
2. During lactation, the ovarian cycle is suppressed. This suppression, as shown by the work of Kurzrok, Lass, and Smelser, is incomplete during lactation menstruation. During lactation amenorrhea this inhibition, as shown by this investigation, is complete.
3. The inhibition of ovarian activity results from suppression of the gonadotropic activity of the hypophysis, as is shown by animal experimentation.
4. The suppression of pituitary gonadotropic activity, in turn, is due to the action of prolactin or else to an internal secretion of lactating mammary gland not as yet isolated.

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118 EIGHTH AVENUE

Stevenson, Stuart S.: Possible Ariboflavinosis in a Premature Infant, *Yale J. Biol. & Med.* 14: 6, 1942.

A premature, 1990 Gm. infant, born of a white mother and Negro father, is reported to have developed yellow incrustations at the mucocutaneous border of the lips on the thirteenth day of life. The baby was fed on half skimmed milk formula, with dextro-maltose added. In addition the infant received orange juice and oleum percomorphum. After observation for two days, treatment with 3 mg. of riboflavin daily was started. The lesion largely disappeared in twenty-four hours. The infant was discharged well at four and one-half weeks. No riboflavin excretion tests were done.

L. M. HELLMAN

THE KRUKENBERG TUMOR

A Critique, With the Report of an Additional Four Cases, Including the Smallest on Record

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FREDERICK KRUKENBERG,¹ in 1896, described a peculiar type of ovarian tumor, theretofore unknown, which has since become associated with his name. He described five cases at that time under the title of "fibrosarcoma ovarii mucocellulare carcinomatodes" and stated that the tumor was usually bilateral, of considerable dimensions, maintaining the form of the ovary, of myxomatous appearance and frequently accompanied by ascites. Microscopically, the structure presented a characteristic "signet ring" cell, spread out between a richly cellular connective tissue stroma so as to suggest an origin from stroma cells or endothelium. Krukenberg was of the opinion that this type of growth represented a primary tumor of the ovary, endothelial in origin and was a type of sarcoma. He failed to note the close resemblance of these tumors to secondary carcinoma of the ovary.

In 1902, Schlagenhauser,² closely followed by Wagner³ and Römer,⁴ stated that the Krukenberg tumor could be reproduced by secondary carcinoma from the abdominal organs and that the great majority of such ovarian tumors are secondary to tumors in other organs. This observation was modestly stated, for relatively few primary Krukenberg tumors have been reported, notably those by Schenk,⁵ Glockner,⁶ Marchand,⁷ Sternberg,⁸ Frankl,⁹ Neumann,¹⁰ Rosthorn,¹¹ Miner,¹² Outerbridge,¹¹ and Andrews.¹² Ewing¹³ states, "I believe that the pure Krukenberg tumor is always secondary and that the primary carcinomas presenting this structure regularly yield areas of a different type." However, it does appear that there is a primary type of Krukenberg tumor and the most recently reported, that of Andrews,¹² was substantiated by studies of Novak.¹⁴

Schlagenhauser² also revealed that the Krukenberg tumor was not a sarcoma but a carcinoma and that it was of epithelial origin. The typical Krukenberg tumor which he observed was a metastatic growth from a mucous cell carcinoma of the pylorus. Kaufman¹⁵ has found "Krukenberg tumors" of the ovary at autopsy and from that finding predicted that an occult primary carcinoma of the stomach was present. This type of observation has not been unusual, for such instances have been reported by Stiekel,¹⁶ Cohn,¹⁷ Hussy,¹⁸ Sandrock,¹⁹ Paul,²¹ Ulesko-Stroganoff,²⁰ Hartman and Metzger,²¹ and van der Perk.²² In one of the original cases described by Krukenberg the patient was operated upon two years later for a tumor of the uterus and revealed the same type of structure as present in the original ovarian growth.

Schlagenhauser² quoted this case in 1902. Major²³ reported a Krukenberg tumor of the ovary which appeared to be primary at the time of autopsy but serial sections of the stomach revealed a gastric carcinoma. Because of such instances as the above, Polanno²⁴ and Papaioannou²⁵ are of the opinion that some skepticism should be manifested in relation to many tumors which have been described as primary endotheliomas of the ovaries.

Incidence

There appears to be a marked increase in the incidence of the Krukenberg tumor. Several factors should be analyzed before any conclusion can be made. Major,²³ in a survey of the literature up to 1918, reported 55 authentic cases and Fallas²⁶ brought the survey up to 1929 by reporting 23 additional cases thus making a total of 78 cases in the thirty-three years following Krukenberg's classic treatise. Since this time, there have been 77 cases reported, including the four in this paper, over a period of thirteen years. It is easy to visualize that about 50 per cent of the cases in the literature have occurred in the past thirteen years of a forty-six-year period. This increase may be due to any one or a combination of several factors. Autopsies are increasing in number. More medical journals exist today than formerly and more reports are written. There appears to be an increase in the incidence of carcinoma of the stomach, and since this is the predominant primary site for Krukenberg metastases, it is only logical to assume the incidence of metastases to be higher.

The tumor can appear at any age; the youngest on record is Chapman's case,²⁷ occurring in a girl of fourteen years. One patient in our series was sixty-six years of age, the oldest on record. It is logical to assume that most cases will occur in that age group in which the most frequent primary tumor, namely carcinoma of the stomach, is likely to appear. It has been suggested by Shaw²⁸ that ovaries of women in the child-bearing period offer a most fertile field for carcinoma cells and that their connective tissue stroma can react in an extraordinary embryonic manner to the presence of cancer cells in the neighborhood. However, the previous explanation appears more reasonable.

Race does not play an important role, for cases have been reported in the black race as in the white. No reports have emanated from the yellow race. Gordon²⁹ reported one of the earlier cases occurring in a Negress; however, it does appear to be less frequent in the colored race.

The incidence of the tumor is as high in single as in married women, and multiparity does not appear to play a role.

Pathology

Gross.—The tumor usually occurs bilaterally and as a rule is of moderate or large size; however, at times these growths may be so small that they are overlooked grossly as is demonstrated in this paper. While they maintain to a marked degree the general shape of the ovary, lobulation

is at times present, sometimes associated with cystic areas. The surrounding capsule is usually smooth outwardly and does not become adherent to surrounding structures. The cut surface varies in appearance and texture, being firm to spongy in consistency with myxomatous or gelatinous areas. At times there may be cyst formation or degenerative changes with hemorrhage.

Microscopic.—Krukenberg placed emphasis on small or diffuse groups of large polyhedral or rounded cells with mucoid contents, compressing the nucleus into a signet ring shape. In the diffuse areas, the cells are intimately mingled with the stroma, suggesting origin from stroma cells or endothelium. This fact caused Krukenberg to mistake the origin of the tumor as was previously pointed out. Actually the microscopic picture is quite as variable as that of the gross. The stroma may be firm, richly cellular, edematous, or genuinely myxomatous; the epithelial elements occurring as clusters of acini, though always in the true Krukenberg tumor showing varying degrees of mucoid changes. The mucoid material at times breaks through the cell membranes and becomes scattered in the stroma. The original gland pattern may be entirely blotted out in certain areas. The feature most often stressed in the microscopic picture is the signet ring cell engorged with mucoid material as described by Krukenberg originally.

The four cases presented show various characteristics of the Krukenberg tumor which will be commented upon following each report.

CASE 1.—Miss A. C., a white female, 66 years of age and unmarried, was admitted to Charity Hospital on Dec. 18, 1937, with a chief complaint of profuse vaginal bleeding. She had not menstruated in the past twenty years. She had suffered from chronic cholecystitis for the past ten years and had lost 30 to 40 pounds in the past six months. Vaginal examination revealed a uterus that was enlarged and fixed. The cervix uteri was smooth and not eroded. A small mass was palpable in the right lower quadrant. The preoperative diagnosis was carcinoma of the body of the uterus. Operation on Dec. 21, 1937, revealed ascites, a stomach that was atrophied and infiltrated with a scirrhus type of malignancy. The uterus was slightly enlarged and displaced toward the right by a large right ovarian tumor. The entire peritoneal cavity was involved by the malignant seeding and the wound was closed. The patient died on Jan. 7, 1938. Autopsy revealed a scirrhus carcinoma of the stomach (Fig. 1) with carcinomatosis of the peritoneal cavity. The right ovary was the only one involved by metastases. Grossly, it still maintained the shape of the ovary. Sections revealed hyperplasia of the normal elements. Throughout the section were seen large, pale, signet ring cells with the nucleus at the periphery (Fig. 2). Other areas within the ovary showed a slight glandular arrangement of malignant epithelial cells.

Comment

This case demonstrates the variation in age wherein one may encounter the Krukenberg tumor. The primary lesion, the stomach, was not recognized and the presenting symptoms were presented by a metastatic site,

the ovary. This is not unusual, for Leffell, Jr., and others³⁶ reported such an occurrence in 14 instances out of a possible 44.

CASE 2.—Mrs. M. P., a white female, 35 years old, was admitted to Charity Hospital on Sept. 4, 1939. She was previously in the hospital on June 13, 1939, and was diagnosed as having a bleeding gastric ulcer.

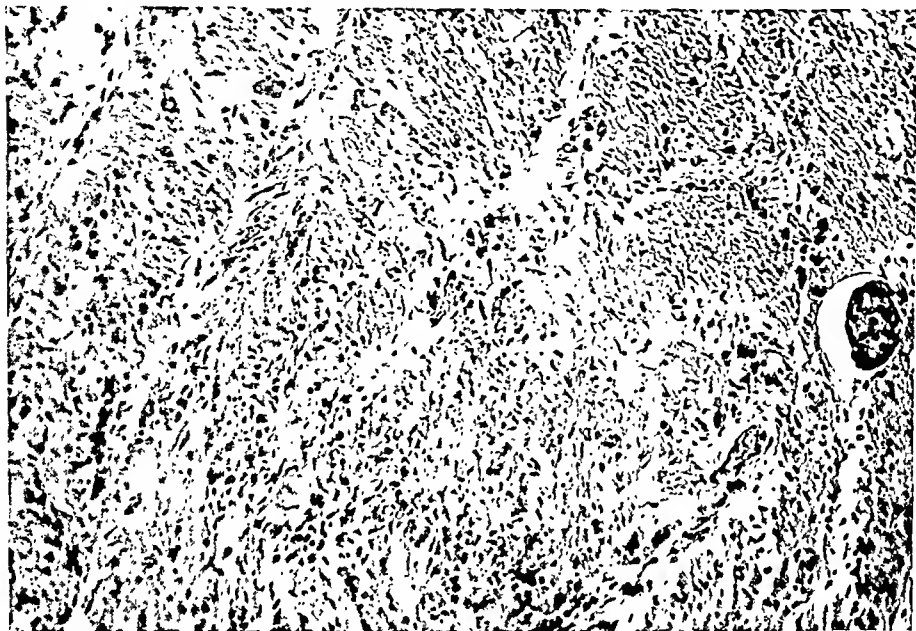


Fig. 1.—Scirrhous carcinoma of stomach producing Krukenberg tumor in Fig. 2. Note single cancer cells in fibrotic stroma (low power).

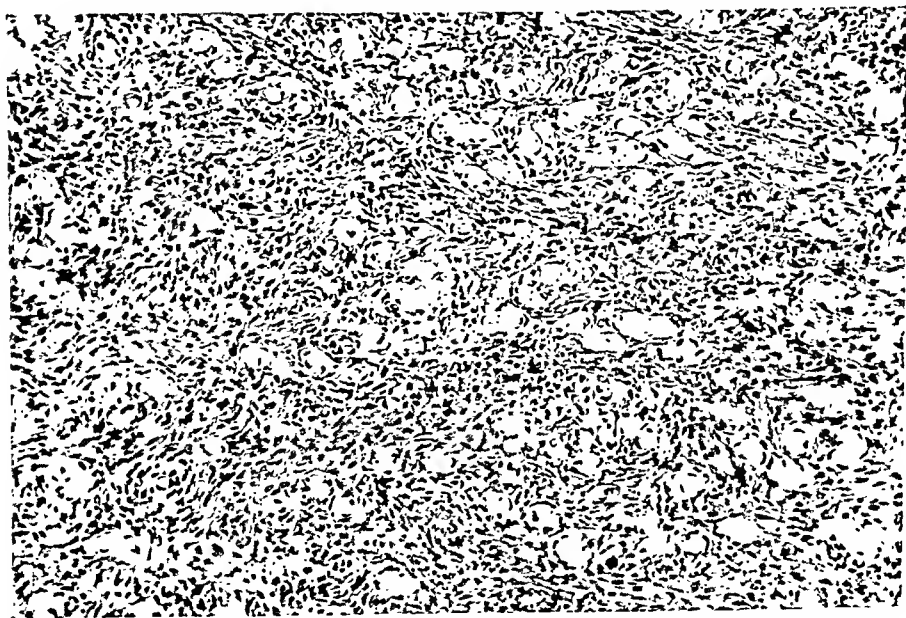


Fig. 2.—Large signet ring cells in Krukenberg tumor secondary to scirrhous carcinoma in stomach (low power).

At that time the diagnosis was confirmed by x-ray, and she was placed on an ulcer regime. One month later, she was seen in the Gynecological Clinic and a diagnosis of "ovarian cyst, most probably papillo-cyst adenoma" was made. On Sept. 7, 1939, a laparotomy was performed. Ascites was present. Carcinomatosis of the peritoneal cavity was present. A bilateral salpingo-oophorectomy was done. The specimen consisted of two ovaries and two tubes, very much enlarged and consisting for the most part of tumor tissue which was firm in consistency, grayish white, and possessing a gray nodular outer surface. Cut sections of the tumor areas showed the outer border to be composed of yellowish white tumor. The inner portion was edematous, cystic, and also appeared to contain areas of malignancy. Attached to both of these

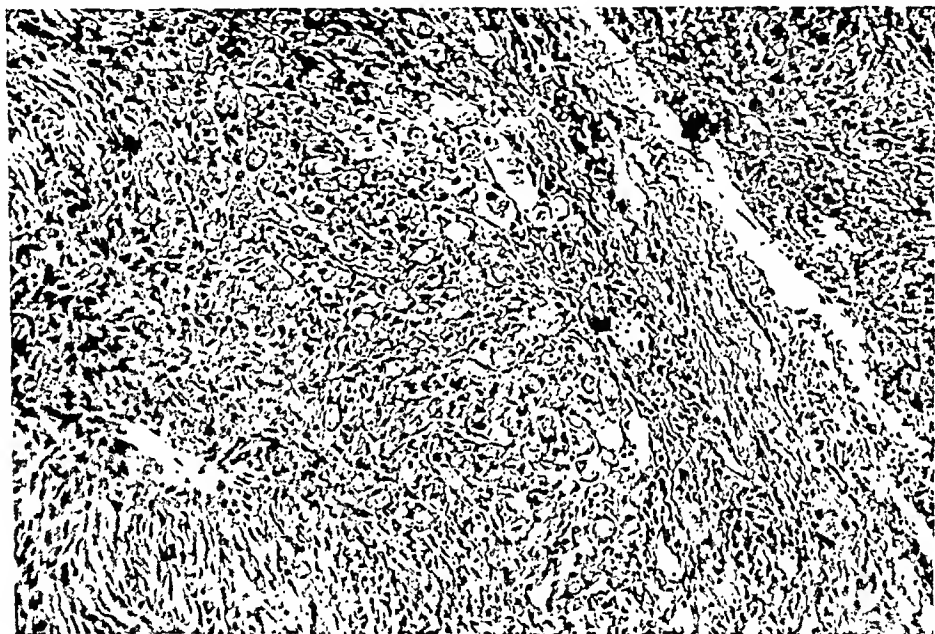


Fig. 3.—Signet ring cells in Krukenberg tumor secondary to gastric carcinoma diagnosed by x-ray (low power).

tumors were two large cystic areas lined with edematous, hemorrhagic walls. The inner lining also showed some small white nodules. The tubes were firm, and the fimbriated ends were somewhat patent. Microscopic sections revealed a highly malignant tumor possessing the structure of a Krukenberg tumor (Fig. 3).

Comment

Even after operation, the diagnosis was considered to be a papillo-cyst adenoma of the ovary, and it was not until the pathologic report was made, that the correct diagnosis was made. After the pathologic report was available, a gastrointestinal x-ray series was made and revealed a carcinoma of the stomach. This case reveals the rapidity of metastasis, for an x-ray of the stomach only thirty days previously was negative for malignancy. It is plausible that at the very time of the x-ray the ovaries were already involved. Again, this case demonstrates that one should beware of ovarian pathology associated with peptic ulcer.

CASE 3.—Miss V. D., a 24-year-old white female, was admitted to Touro Infirmary on July 25, 1936, with a diagnosis of acute pelvic peritonitis. She was treated conservatively, and died six days later. Autopsy revealed that the primary cause of death was an adenocarcinoma of the rectum with a perforation and peritonitis.



Fig. 4.—Rectal carcinoma giving rise to bilateral Krukenberg tumors (Fig. 5). Note tendency to form signet rings in primary tumor (low power).

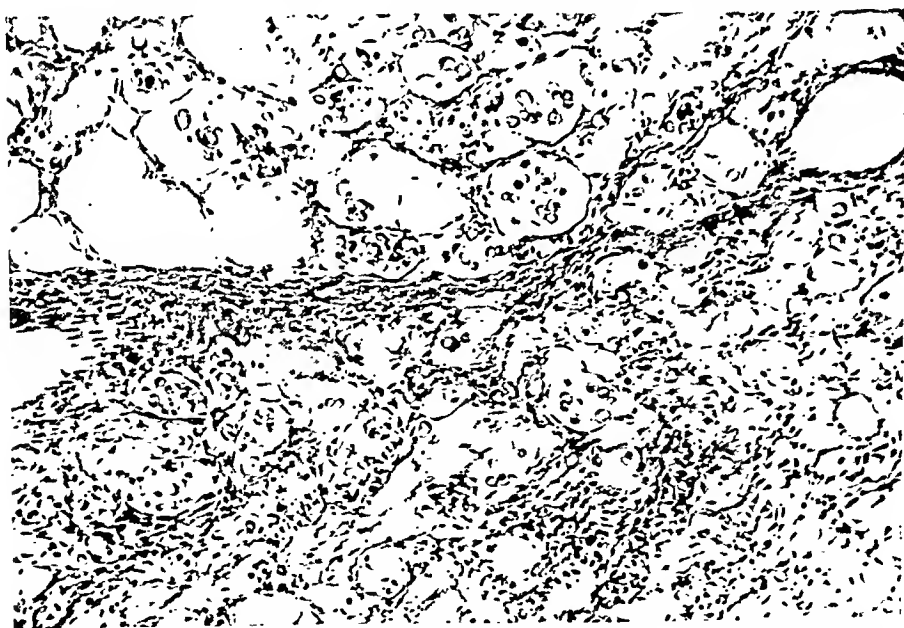


Fig. 5.—Typical Krukenberg tumor, same in both ovaries, from primary rectal carcinoma (low power).

During the course of a complete autopsy, the ovaries were found to be replaced by two large tumors. The tumors were firm in consistency and quite irregular. The external surface was covered with purulent material. The right tumor measured 11 by 5 by 6 cm. and the left measured 6 by 4 by 6 cm. The tumors cut with increased resistance and the cut surfaces were yellowish white in color and very gelatinous. It appeared quite cellular. Histologic sections through the primary rectal tumor (Fig. 4) showed the presence of typical colloid carcinoma with some attempt at signet ring formation with glandular acini bathed in mucus. Sections through the ovarian tumors (Fig. 5) showed an edematous stroma supporting numerous signet ring cells and occasional glandular acinar formations. The cell type was characteristic of Krukenberg's tumor.



Fig. 6.—Scirrhous carcinoma of stomach giving rise to bilateral small Krukenberg tumors (Figs. 7 and 8) (low power).

Comment

The primary site varies in this instance, the rectum being the original focus. Cases have been reported secondary to growths in the gall bladder, small intestines, large intestines, stomach, and breast. However, the stomach is the primary focus in the prepondering majority of instances. This is so true that when one considers whether or not a malignancy of the abdominal viscera is operable or not, one should palpate the ovaries to determine if metastases are present.

CASE 4.—Miss B. L., 36 years of age, was admitted to Touro Infirmary on July 6, 1941, with a diagnosis of carcinoma of the stomach. Her first gastric complaint occurred only three weeks previously on June 14, 1941. At operation, a diffuse linitis plastica type of gastric malignancy was found, and a subtotal gastrectomy was performed. Histologically, the growth was a scirrhous carcinoma (Fig. 6). The patient died on Aug. 7, 1941, thirty-two days after admission and forty-three days after the

first gastric symptoms had occurred. Autopsy revealed some malignant infiltration of the head of the pancreas. The ovaries were small, wrinkled, and presented some cystic areas, a thickened tunica albuginea and marked increase in fibrosis, the fibrosis grossly creating the picture similar to atrophic changes in the ovary. In both ovaries, on microscopic examination, were small Krukenberg tumors (Fig. 7) measuring approximately 3 mm. in diameter. The signet ring cells making up these

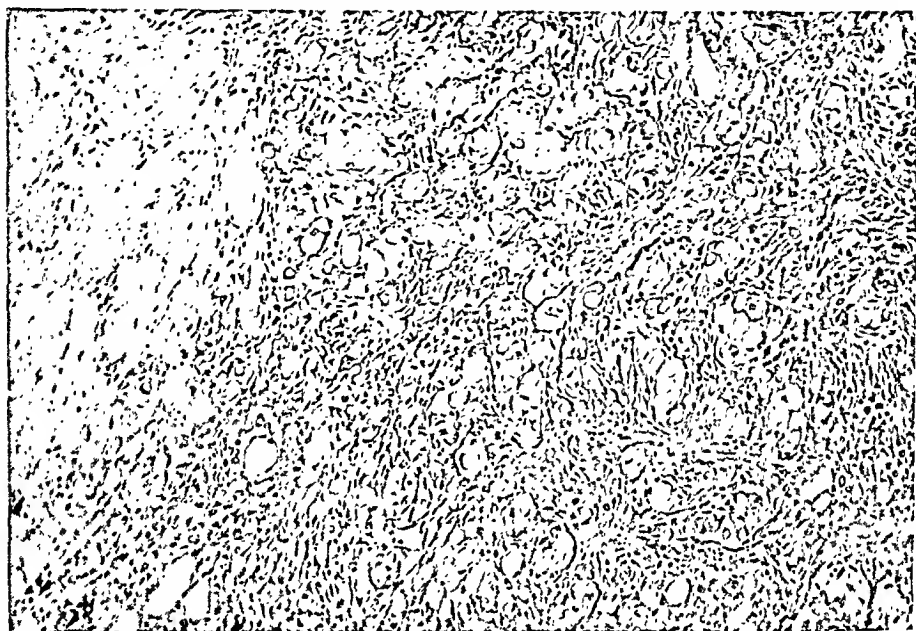


Fig. 7.—Krukenberg tumor (3 mm. gross) secondary to scirrhus carcinoma of stomach.

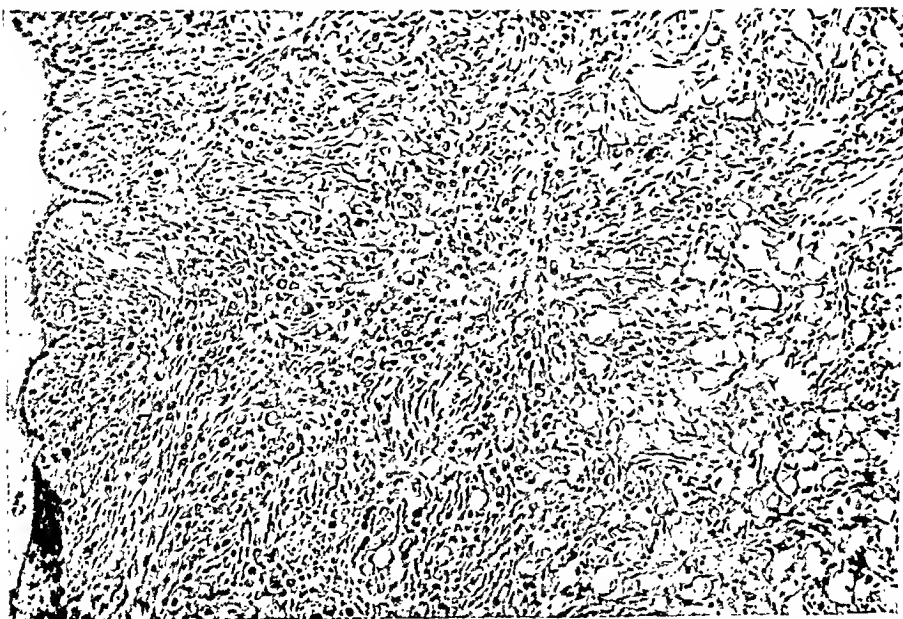


Fig. 8.—Krukenberg tumor secondary to scirrhus carcinoma of stomach. Note intact germinal epithelium (low power).

tumors were identical with some found in the gastric carcinoma. The germinal epithelium covering the ovary in the section appeared to be intact (Fig. 8).

Comment

These Krukenberg tumors are the smallest on record to our knowledge and were discovered accidentally for the sectioning of the ovary could easily have escaped passing through a 3 mm. growth. Again, the remarkable rapidity of a Krukenberg metastasis is demonstrated, for this one was discovered forty-three days after the initial subjective complaint due to the primary growth. With the increasing incidence of gastrectomy, one must be more cognizant of ovarian metastases, and the surgeon should palpate the ovaries before classifying the gastric growth as having not metastasized. Ascites is not essential to metastasis. The fact that the tunica albuginea was thickened and intact immediately causes one to think that the route of metastasis was not by continuity of tissue but by either the lymphatic or blood stream. In this instance the histology of the original growth in the stomach mimicked the structure of the ovarian Krukenberg tumor. This has not been the pattern that is always followed and which has been so admirably discussed by Novak¹⁴ who states, "When the primary gastrointestinal tumor is of the mucoid type it is natural to expect the ovarian metastasis to have the same characteristics. On the other hand in a considerable number of reported cases, as well as in a number of our own, the primary tumor shows no suggestion of mucoid change. Scirrhus carcinomas, and even linitis plastica, have constituted the primary foei in many cases in which, when transplanted to the ovary, the growth has developed highly mucoid characteristics. After all, this need not be wondered at for mucoid changes are frequently noted in scattered areas of gastrointestinal cancers of primarily and dominantly nonmucoid type, not only of the gastrointestinal tract but also of the gall bladder, or breast, either of which may constitute the primary seat of the malignancy in Krukenberg tumors."

A very controversial phase of the Krukenberg tumor has been the route of metastasis from the primary growth to the ovary. There are four possible avenues of metastasis: (1) Lymphatics, (2) blood stream, (3) implantation of cancer cells on the ovarian surface by peritoneal fluid, (4) direct continuity of tissue. The first possibility is a very logical one and appears to be the mode of transmission in the majority of cases. Amann³⁰ theorized that the retrogastric and superior lumbar lymph nodes are invaded and produce an obstruction of the lymphatic stream and as a result there is retrograde migration by the ovarian lymphatics. This theory appears all the more plausible for the shape of these secondary tumors, even when quite large, almost invariably conforms to the original shape of the ovary, as though the invasion were through the medulla rather than the cortex. This is true in Case 4 of our series, wherein a 3 mm. growth is present in the medulla with a thickened, unbroken cortex. However, the possibility of metastases being borne through the blood stream cannot be eliminated, especially in the face of such evidence as presented by Major,²³ wherein typical Krukenberg cells were found in the pulmonic blood vessels of a patient dying of a Krukenberg tumor. In patients presenting a markedly advanced carcinomatosis of the peritoneal cavity, one visualizes the modus operandi as occurring from cancer cells being implanted on the various organs by the ascitic fluid. It is difficult to conceive that in the early

case, wherein only the stomach and ovary are involved, the cells are carried solely to the ovary and no other organ. It is beyond probability that such a selective affinity exists. The last mentioned route, continuity of tissue, does not appear logical in most cases. This mode of transmission does appear feasible if the original growth is in a loop of intestine that is in direct contact with the ovary.

Summary

1. The Krukenberg tumor is a primary or secondary tumor of the ovary of epithelial origin, usually bilateral, in which the ovary maintains its original shape and is frequently accompanied by ascites.

2. A primary Krukenberg tumor is rare and can only be classified as such after microscopic examination of the various viscera, especially the stomach, from which it may metastasize.

3. The typical cell of the Krukenberg tumor is the signet ring cell.

4. The route of metastasis is most probably through the lymphatic or blood stream.

5. The ovaries should be examined before the surgeon classifies an intestinal tract malignancy as not metastatic.

6. The incidence of the Krukenberg tumor appears to be increasing.

7. The primary growth need not possess the same structure as the Krukenberg metastasis in the ovary.

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SWALLOWING AND GASTROINTESTINAL ACTIVITY IN THE FETAL MONKEY

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IN CONTRAST to the vast and growing body of knowledge relating to the physiology of the adult, observations on the functions of the various organic systems of the fetus are as yet fragmentary and incomplete. The gastrointestinal system is no exception, for despite the sporadic interest which has been accorded fetal gastrointestinal activity for at least half a century, the total knowledge which has been amassed is, at best, meager. The technical difficulties of experimentation on fetuses without seriously compromising their homeostasis have been largely responsible for the tardy progress which has been made.

The present report extends to the rhesus monkey observations of swallowing and gastrointestinal activity which have been made on fetuses of other species, by a highly physiologic although not original technique.

In the classical monograph published by Preyer in 1885, which summarized the available knowledge of fetal physiology at that time, mention is made of the frequent finding of hair in the stomachs of newborn calves and occasionally of fetal guinea pigs. Never were the stomachs of term chicks found empty. Morrigia is said to have found hair in the meconium of cattle fetuses; and mention is made of the observations of Crepin, who found in the stomach of a horse fetus aged seven or eight

months a large amount of horny material of the same composition as hoofs. Preyer came to the conclusion that not only was swallowing a normal fetal function, but that the amniotic fluid when swallowed plentifully served as a food for the fetus.

Several experimental techniques have been used in attempts to demonstrate gastrointestinal activity in various embryonic and fetal forms. Urbach (1924) injected a suspension of powdered lycopodium into the amniotic sac of chicks at different stages of development and sought the powder in the gastrointestinal tract after various periods of time. Gastrointestinal motility was found to increase with the age of the chick embryo. At seven days, for example, no powder was found in the gastrointestinal tract after forty hours, whereas at sixteen days powder was present in the stomach in one hour and in the intestines three hours after injection. A similar experiment, performed on a twenty-three-day-old rabbit fetus, revealed the powder in the stomach and intestines after twenty-four hours.

Other authors, employing different techniques, have likewise demonstrated the swallowing of amniotic fluid and intestinal motility in the fetal rabbit. Zuntz (1878), for example, administered a saturated solution of sodium indigosulfate intravenously to pregnant rabbits. The dye subsequently appeared in the amniotic fluid and in several cases in the stomach contents of the fetus, but no other fetal organs were stained blue. Despite the very slow injection of the dye into the maternal animal, however, the result was invariably fatal to the mother. Similar experiments on rabbits were performed by Wiener (1881), using more dilute solutions of the same dye. In the fetuses of rabbits killed at various intervals up to one hour after injection during the latter half of pregnancy, the dye appeared in the amniotic fluid, stomach, and intestines. Little or none of the dye passed into the amniotic fluid during the first half of pregnancy. The same author (Wiener, 1883) injected calcium ferrocyanide directly into the amniotic sacs of anesthetized pregnant rabbits and dogs. The fetuses were observed to make swallowing movements, and after two or three hours the substance was demonstrated in the stomach and intestines by means of the Prussian blue reaction. Tani (1927) was able to obtain kymographic tracings of the spontaneous stomach movements of the rabbit fetus weighing 7.5 Gm. As the weight increased the movements became more distinct and wider in amplitude.

Spontaneous contractions of the stomach have likewise been observed in the fetal cat of 58 mm. Friedman (1936) detected peristaltic and antiperistaltic waves and demonstrated the effects of acetylcholine, pilocarpine, atropine, and adrenalin. Windle and Bishop (1939) have also demonstrated prenatal intestinal movements in the cat under conditions of rather marked anoxia. Fetuses delivered with the placental circulation intact showed peristaltic movements of the stomach as early as

the 35 mm. stage, strength of the peristaltic waves increasing in fetuses up to 70 mm. body length.

The most complete observations of fetal alimentary activity are those on the guinea pig. Yanase (1907) removed guinea pig fetuses at various stages of development and observed intestinal peristalsis as early as the twenty-sixth or twenty-seventh day. Spontaneous gastric and intestinal peristalsis were also observed by Becker and Windle (1941) in the 35 mm. (thirty-five days old) fetal guinea pig which had been delivered in a bath of Locke's solution at 37° C. with the placental circulation intact, anesthesia of the maternal animal having been achieved by anemic decerebration. Peristalsis became progressively more active throughout the gastrointestinal tract up to about fifty days, but diminished thereafter in the small intestine. Wislocki (1920) injected soluble and colloidal dyes directly into the amniotic sac of anesthetized guinea pigs during the latter part of gestation. Examination of the fetuses revealed the coloring matter in the stomach one hour after injection; after a somewhat longer period the dye appeared in the intestines also. Similar observations were also made upon a few cat fetuses near term.

The clearest demonstration of the physiologic nature of swallowing, gastrointestinal peristalsis, and defecation by the fetal guinea pig is found in the well-illustrated recent paper by Becker, Windle, Barth, and Schulz (1940). These authors injected 0.4 to 1 c.c. of a colloidal suspension of thorium hydroxide or thorium dioxide into the amniotic sac of unanesthetized pregnant guinea pigs after withdrawing an equal volume of amniotic fluid. By means of serial roentgenograms it was possible to trace the course of the radiopaque thorium through the alimentary canal. The first stomach shadows were detectable at forty-two days' gestation. The rapidity with which the thorium reached the fetal stomach increased with age. At forty-two days, for example, thirty-six hours were required, whereas at term (sixty-six to sixty-seven days) x-ray visualization of the fetal stomach was possible two hours after injection. The rate at which the intestinal contents were propagated likewise increased with the stage of pregnancy. Defecation into the amniotic sac and subsequent meconioophagy were observed as normal occurrences in the guinea pig during the last week of pregnancy. These phenomena are apparently uncommon in other species (Windle, 1940), although defecation *in utero* has been demonstrated in a human fetus of 5½ months (Szendi, 1940).

Observations on the human, although scant, are qualitatively in agreement with those made on the rabbit, cat, and guinea pig. Spontaneous rhythmical movements have been observed in fetal stomachs of thirteen to nineteen weeks' gestation age (Tani, 1927) and in the excised intestine of a human fetus of eleven weeks (Yanase, 1907). Subsequent studies have been based on the roentgen visualization of the

fetal stomach after the injection of radiopaque materials into the amniotic sac. Menees, Miller, and Holly (1930) were the first to demonstrate the feasibility of this procedure by means of x-rays after the injection of strontium iodide into the amniotic sac through the intact abdominal wall of the mother. Ehrhardt (1937, 1939) later injected 8 c.c. of colloidal thorium into the amniotic sac of a twenty-one-year-old girl fifteen hours before subjecting her to abdominal hysterotomy at about the sixth month of pregnancy. A roentgenogram of the fetus after delivery revealed thorium in the stomach and intestines. This author (Ehrhardt, 1941) has more recently reported similar findings in other human fetuses of three to six months' gestation age. Reifferscheid and Schmiemann (1939) likewise injected a radiopaque thorium compound into the amniotic sac of a fetus aged five months. Roentgenograms taken thirty and forty-eight hours later, before and after abdominal hysterotomy, respectively, revealed dense shadows of the stomach and intestines. By this technique regions of the gastrointestinal tract of the human fetus have also been outlined by Cetroni and Azzariti and by Albano and Gallina. Szendi has even claimed the roentgen visualization of the fetal stomach as early as eight or ten weeks' gestation age (C. R. 9.5 cm.), forty-four hours after the injection of thorotrast.

Studies such as these, together with the commonly observed presence of vernix caseosa and lanugo hair in human meconium, have left little doubt as to the physiologic occurrence of swallowing of amniotic fluid by the human fetus. De Snoo (1937) has even claimed the successful alleviation of hydramnios by the injection of saccharin into the amniotic sac of pregnant women, the sweetened amniotic fluid presumably inducing the fetus thereby to drink more of it.

Interpretations based on the results of the animal experiments must take into consideration the modifying effects of the experimental conditions. As Windle and his co-workers have pointed out, these conditions have frequently caused serious aberrations from the physiologic state of the organism. The factors of anesthesia, laparotomy, anoxia, and the toxicity of the injected test substances to both mother and fetus may all have vitiated conclusions as to the normal functioning of the fetal alimentary tract in utero. For these reasons, only the work of Ehrhardt, of Reifferscheid and Schmiemann, of Szendi, and of Menees, Miller, and Holly on the human, and of Becker, Windle, Barth, and Schulz on the guinea pig can be considered as demonstrations of the normal functions of the gastrointestinal tract of the fetus. The injection of small quantities of radiopaque media into the amniotic cavity with subsequent roentgen visualization of its contents is regarded as less disturbing to the normal fetal environment than any of the other techniques employed.

It has therefore seemed of interest to record some observations of fetal swallowing and gastrointestinal activity in the rhesus monkey which were made, using the same technique, in the course of recent experiments designed to study fetal respiratory movements in this species.

Experimental

The following observations are based upon 18 roentgenograms of 4 rhesus monkeys at various stages of gestation between 99 and 158 days. Since the animals were mated under controlled conditions in the laboratory, the duration of pregnancy was accurately known in each instance. The actual stages represented are as follows: 99, 102, 134, 139, 142, 144, 147, 148, 155, 156, 157, and 158 days. The unanesthetized animal was held in the supine position and the abdomen shaved and prepared with soap, water, and alcohol. A 19-gauge intravenous needle attached to a syringe was inserted through the intact anterior abdominal wall into the amniotic sac and four to twelve c.c. of amniotic fluid slowly aspirated. With the needle still in position, the syringe was detached and replaced by another containing the radiopaque medium, which was then injected at a very slow rate to equal the volume of amniotic fluid withdrawn. Diodrast (a 70 per cent solution of 3,5-diiodo-4-pyridone-N-acetic-diethanolamine) was used in one experiment; in all the others thorotrast (a 25 per cent suspension of thorium dioxide) served as the test substance. Lateral roentgenograms of the maternal abdomen were made at various intervals between thirty minutes and three days following the injection, to visualize the fetus in utero. In two cases roentgenograms were made of the fetus immediately after its delivery by cesarean section at 148 and 155 days, respectively; in a third case after premature labor at 144 days. (Gestation in the rhesus monkey normally averages 165 days.) In two experiments roentgenograms were made before and after fifteen-minute periods of intermittent rebreathing. Protocols of the individual experiments follow:

MONKEY 690.—Feb. 21, 1940, 99 days pregnant. At 3:45 P.M. 5 c.c. of amniotic fluid were replaced by 5 c.c. of thorotrast. A roentgenogram taken at 5:15 P.M., one and one-half hours later, revealed a small faint shadow in the region of the fetal stomach. In another roentgenogram at 8 P.M., four and one-half hours after the introduction of the thorotrast into the amniotic sac, the fetal stomach appeared full and well outlined. In addition a few small shadows were present in several loops of small intestine.

Feb. 24, 1940, 102 days pregnant. At 1 P.M. 4 c.c. of thorotrast were injected into the amniotic sac. A roentgenogram taken one-half hour later showed the fetal stomach to be partially filled and most of the intestinal tract well outlined. The esophagus was not seen. The intestinal thorotrast was believed to be the result of the previous injection.

At 3:20 P.M. the entire gastrointestinal tract, from esophagus to colon, was beautifully outlined in the x-ray picture (Fig. 1). The maternal animal was then forced to rebreathe into a closed anesthetic mask and rubber bag for three five-minute periods in rapid succession. A roentgenogram at 3:50 P.M. revealed no essential change in the gastrointestinal pattern, except that the esophageal shadow was less distinct, with the cardiac end no longer discernible.

On Feb. 28, 1940, the one hundred and sixth day of pregnancy, miscarriage occurred. The fetus was partially eaten by the mother, but the remaining parts appeared well preserved and showed no signs of maceration.



Fig. 1.—Monkey 690, 102 days' gestation age, showing entire fetal gastrointestinal tract following two injections of thorotrast into amniotic sac.

MONKEY 601.—Feb. 16, 1940, 134 days pregnant. This monkey was fluoroscoped at 4 P.M. in an attempt to visualize intrauterine respiratory movements of the fetus. Although general somatic movements were clearly visible, no excursions of the thoracic cage or diaphragm could be detected. A lateral roentgenogram of the maternal abdomen was then made which showed the fetus in breech presentation (Fig. 2).

At 5 P.M. 5 c.c. of amniotic fluid were replaced by an equal volume of diodrast. By 2 P.M. the following day, twenty-one hours later, the stomach and small intestine had apparently completely emptied themselves of the diodrast, for only the large intestine could be visualized (Fig. 3). (Contrast with Monkey 690.)

Feb. 21, 1940, 139 days pregnant. At 3:30 P.M. 6 c.c. of amniotic fluid were replaced with an equal volume of thorotrast. A roentgenogram at 5:15, one and three-quarters hours later, showed the material distributed in several loops of small intestine with the stomach very faintly outlined (Fig. 4). In another x-ray photograph at 8 P.M., two



Fig. 2.—Monkey 601, 134 days' gestation age.

and three-quarters hours later, the intestinal shadows appeared much denser (Fig. 5). Since the same technique was employed in making both roentgenograms, the increased density of the intestinal shadows in the latter may be attributed to a concentration of the thorotrast resulting from the absorption of water by the small intestine.

Feb. 24, 1940, 142 days pregnant. At 12:45 P.M. 7 c.c. of amniotic fluid were again replaced by an equal volume of thorotrast. A roent-

genogram at 1:30 P.M., forty-five minutes later, revealed the substance in the fetal stomach and intestines, but the details could not well be made out. At 3:25 P.M., two hours forty minutes after injection, the thorotrast was distributed between the small and large intestines. The maternal animal was then forced to rebreathe for three successive five-minute periods. No significant change in the intestinal pattern could be demonstrated in a roentgenogram made at 4:05 P.M.

Feb. 26, 1940, 144 days pregnant. A 400 Gm. stillborn female infant was prematurely delivered. The thorotrast may be seen concentrated in the large intestine (Fig. 6).

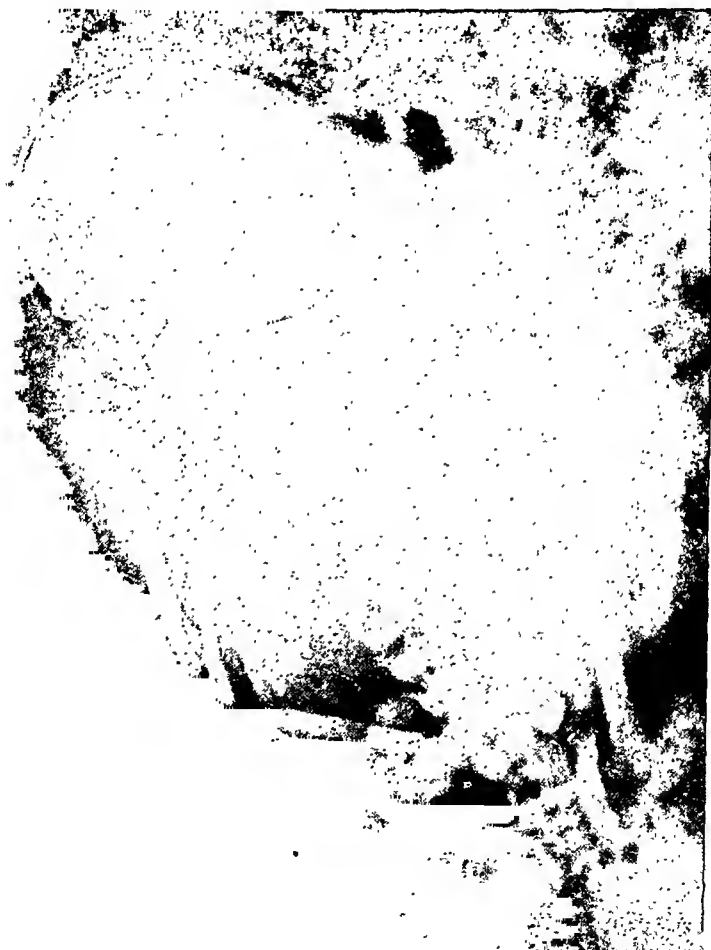


Fig. 3.—Same as Fig. 2, twenty-one hours after injection of diodrast into amniotic sac.

MONKEY 651.—May 27, 1940, 147 days pregnant. At 10 A.M. 12 c.c. of amniotic fluid were replaced by an equal volume of thorotrast. At this time active fetal movements could easily be felt through the intact abdominal wall of the mother. A roentgenogram made at 5 P.M., seven hours later, revealed the stomach and many loops of the intestinal tract filled with the thorotrast (Fig. 7).

On May 28, 1940, twenty-four hours after injection, cesarean section was performed under intravenous nembutal anesthesia. A male fetus was removed with the entire amniotic sac intact. Rhythmical respiratory movements were clearly discernible through the unopened amniotic sac after its removal from the uterus. These persisted for several minutes. The amniotic sac was opened five minutes after the respiratory movements ceased. The fetus then made several gasping and swallowing



Fig. 4.—Monkey 601, 139 days' gestation age, one and three-quarters hours after injection of thorotrast into amniotic sac.

efforts at about two-minute intervals for the next ten minutes. The entire pharynx was then tightly packed with cotton and a roentgenogram made of the fetus. The large intestine was completely filled with thorotrast, with little or none in the small intestine. A small, somewhat fainter shadow, surrounded by a large air bubble, outlined the stomach (Fig. 8).

MONKEY 715.—March 4, 1941, 155 days pregnant. Twelve cubic centimeters of thorotrast were injected into the amniotic sac after the

withdrawal of an equal volume of amniotic fluid. A roentgenogram approximately twenty-four hours later showed the stomach and small intestines only partially outlined by the thorotrast. The large intestine, by contrast, contained large amounts of the test substance. In the roentgenogram taken twenty-four hours later the stomach and small intestine could no longer be seen, and the thorotrast was completely concentrated in the large intestine.



Fig. 5.—Same as Fig. 4, two and three-quarters hours later. Note concentration of thorotrast in intestine.

On March 7, 1941, at 158 days' gestation and approximately 72 hours after the injection of thorotrast, cesarean section was performed under intravenous nembutal anesthesia. The infant's neck was firmly clamped as soon as possible, so as to compress the trachea and esophagus completely and thereby prevent extrauterine inspiration or swallowing. A roentgenogram showed the large intestine to be full of thorotrast, but no other parts of the gastrointestinal tract could be visualized in the film. No air was present in either the lungs or stomach.

Comment

Results of the foregoing experiments clearly demonstrate the occurrence of swallowing and the propagation of gastrointestinal contents in the monkey fetus in utero. The amniotic fluid reaches the large intestine within twenty-four hours after being swallowed near term, as indicated by the presence of dense shadows in the roentgenogram fol-



Fig. 6.—Same as Fig. 4, after premature delivery at 144 days' pregnancy. Thorotrast is concentrated in large intestine.

lowing the administration of thorotrast. There is no indication, however, that defecation normally occurs in utero, for the thorotrast has been observed filling the large intestine and redundant sigmoid after periods ranging up to seventy-two hours following the last injection (Monkeys 601 and 715; Figs. 6 and 8). Although the solid constituents of the amniotic fluid are retained in the large bowel, water is apparently resorbed very rapidly from the intestine. This is shown by the rather marked increase in the density of the intestinal shadows cast by the thorotrast in roentgenograms taken two and three-quarters hours apart (Monkey 601; Figs. 4 and 5).

The present findings are in agreement with the previous studies on fetuses of other species which have demonstrated an increase in gastro-



Fig. 7.—Monkey 651, 147 days' gestation age, showing stomach and intestines seven hours after injection of thorotrast into amniotic sac.



Fig. 8.—Same as Fig. 7, after delivery by cesarean section twenty-four hours after injection. Thorotrast is concentrated in large intestine. Note air in stomach; this resulted from swallowing after delivery of fetus from amniotic sac.

intestinal motility and rate of propagation of gastrointestinal contents with the advance of pregnancy. In Monkey 690, for example, at 99 days' pregnancy only a faint stomach shadow could be detected one and one-half hours after the injection of thorotrast, whereas in Monkey 601 at 139 days' gestation many loops of small intestine were filled with thorotrast one and three-quarters hours after administration of the test substance. In Monkey 690, at 102 days' gestation, the fetal stomach was still full of thorotrast two hours and fifty minutes after injection into the amniotic sac, while the fetal stomach of Monkey 601 had completely emptied itself in less than two hours and forty minutes at 142 days' pregnancy. In contrast to the latter, the fetal stomach of Monkey 651 was still fairly well outlined seven hours after the injection of thorotrast at 147 days' pregnancy. This apparent discrepancy is probably due, however, to the greater volume of thorotrast injected in Monkey 651 (12 c.c. as compared with 7 c.c. in Monkey 601). The fetus may well have refilled its stomach with the excess thorotrast which remained in the amniotic sac and which is plainly visible in Fig. 7. It seems reasonable to conclude, therefore, that in the monkey fetus, in common with those of other species, the rate of swallowing increases and the emptying time of the stomach decreases as pregnancy progresses.

Summary

1. Swallowing and gastrointestinal activity have been demonstrated in the fetal monkey by means of serial roentgenograms following the injection of radiopaque substances into the amniotic sac at various stages of gestation between 99 and 155 days.
2. The rate of swallowing of amniotic fluid increases and the emptying time of the fetal stomach decreases as pregnancy progresses.
3. No evidence was obtained for the normal occurrence of defecation in utero.
4. Water is absorbed by the fetal intestine, thereby producing a concentration of the intestinal contents.
5. Rebreathing by the maternal animal had no demonstrable effect on the rate of propagation of the intestinal contents of the fetus.

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SULFANILAMIDE AND SULFATHIAZOLE THERAPY IN ACUTE SALPINGITIS

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THE sulfonamides have been found to be of value in the treatment of gonorrhea in both the male^{2, 9} and female.^{1, 3, 6, 7} Numerous reports attest to the efficacy of sulfanilamide, sulfathiazole and sulfapyridine in the cure of gonococcal infections below the internal os in the female.

In view of the good results obtained with chemotherapy in treating gonococcal urethritis and endocervicitis, it appeared necessary to investigate thoroughly the effectiveness of the sulfonamides in the treatment of acute adnexal disease. Since the onset of this study several reports^{4, 5, 10} have appeared in literature which discredit the use of these drugs in adnexal disease, although it appears that this form of therapy may be of value in the treatment of the initial attacks of salpingitis before palpable masses have formed.

Method

Every case of acute or chronic adnexal disease admitted to the gynecologic wards of Bellevue Hospital from January, 1941, to May, 1942, was studied. On admission to the hospital smears of the urethra and cervix were examined for the presence of intracellular diplococci. All patients with spreads which were positive for these organisms were treated alternately with either sulfanilamide or sulfathiazole. In order to obtain a control group which would facilitate the evaluation of the effectiveness of chemotherapy, a portion of those patients with negative spreads were observed under simple palliation, whereas the remainder were treated with either sulfanilamide or sulfathiazole.

The sulfonamide was administered for a period of seven days, the series consisting of 1 Gm. four times daily for the first two days; 1 Gm. three times daily for the next three days; and 1 Gm. twice daily for the last two days. Thus each patient received 21 Gm. of either sulfanilamide or sulfathiazole during the one week of therapy. In those instances where the spreads failed to become negative after the first series was completed, a second series of doses was given during a succeeding week. Occasionally, if the patient failed to respond to therapy with the same type of drug during the second series, the other drug was substituted.

Upon the completion of each course of drug therapy, smears of the urethra and cervix were re-examined, and a pelvic examination was performed. Although subsequent pelvic examinations depended upon the course of the disease, every patient was re-examined at intervals of one to two weeks. The final pelvic examination was performed on discharge. The erythrocyte sedimentation time and the red and white blood counts were performed at intervals, as indicated during the course of the disease.

Results

Two hundred and four cases of acute salpingitis were studied during the interval of investigation. Of these, 71 were admitted during their initial attack of acute salpingitis, and 133 during an acute exacerbation of chronic adnexal disease (Table I). Seventy-six cases of adnexitis

TABLE I

A. Acute primary adnexal disease		71
Positive spreads	31 (43%)	
Negative spreads	40 (57%)	
B. Recurrent adnexal disease		133
Positive spreads	45 (33.7%)	
Negative spreads	88 (66.3%)	
Total cases studied		204

(37 per cent) were found to have endocervical and urethral smears positive for the gonococcus. Cultural methods for determining the presence of the gonococcus were not employed because this study was concerned primarily with acute salpingitis and its response to chemotherapy.

TABLE II. EFFECT OF CHEMOTHERAPY ON POSITIVE SPREADS

	NEGATIVE AFTER 1 WEEK THERAPY	NEGATIVE AFTER 2 WEEKS THERAPY	RESISTANT CASES REQUIR- ING OVER 2 WEEKS OF CHEMOTHERAPY
Sulfanilamide (46)	40 (87%)	4 (8.7%)	2 (4.3%)
Sulfathiazole (44)	41 (91%)	3 (9%)	0

Effect of Chemotherapy on Lesions Below the Internal Os.—Table II shows the effect of sulfanilamide and sulfathiazole on gonococcal urethritis and endocervicitis. The results obtained confirm the striking effects of sulfanilamide and sulfathiazole in causing the disappearance of the gonococcus from the urethral and cervical secretions as far as could be determined by the examination of smears. Both sulfanilamide

and sulfathiazole appeared to be equally effective, 87 per cent of positive spreads becoming negative after one week of sulfanilamide therapy as compared with 91 per cent negative spreads after sulfathiazole. A few of the cases (9 per cent) required an additional week of therapy with either sulfanilamide or sulfathiazole before the smears became negative (Table II). Three negative smears on three separate days were required before the negative results were accepted. Two patients (4.3 per cent) continued to have positive spreads after two weeks of treatment with sulfanilamide and these became negative after the third week during which sulfathiazole was administered. Relatively few of this group of patients returned to the clinic, making a prolonged follow-up impossible.

Effect of Chemotherapy on Acute Adnexal Disease.—The effectiveness of any form of therapy varies with the severity and the duration of adnexal disease. Therefore, in order to judge the results of treatment, it became necessary to classify all cases in this study according to (a) the length of time which elapsed from the beginning of the illness before the onset of therapy; (b) duration of the disease as to whether it was a primary or a recurrent attack; and (c) severity of the illness as to whether it was a mild, moderate, or severe attack. All cases which had a mild temperature reaction, tenderness, and adnexal masses under 5 cm. in size were classified as mild. Those showing a greater temperature reaction, adnexal masses over 5 cm. in diameter, and requiring a

TABLE III. EFFECT OF CHEMOTHERAPY ON ACUTE ADNEXAL DISEASE

TYPE	NO. OF CASES	R	CASE WITH MASSES PRESENT ON ADMISSION		CASE WITH NO MASSES PRESENT ON ADMISSION		LAP.†
			COMPLETE RESOLUTION	INCOMPLETE RESOLUTION	IMPROVED, NO MASSES FORMED	UNIMPROVED, MASSES FORMED	
<i>A. Primary acute adnexitis, less than 5 days' duration</i>							
Mild	5	Pall.*	1 (20%)	3 (60%)	1 (20%)	0	0
	10	Chemo.†	7 (70%)	2 (20%)	1 (10%)	0	0
Moderate	0	Pall.	0	0	0	0	0
	9	Chemo.	6 (66.6%)	3 (33.3%)	0	0	0
Severe	1	Chemo.	0	1	0	0	0
<i>B. Primary acute adnexitis, over 5 days' duration</i>							
Mild	3	Pall.	1 (33%)	1 (33%)	1 (33%)	0	0
	19	Chemo.	4 (21%)	8 (42%)	7 (32%)	0	0
Moderate	0	Pall.	0	0	0	0	0
	17	Chemo.	6 (35%)	11 (65%)	0	0	1
Severe	3	Pall.	0	3 (100%)	0	0	0
	6	Chemo.	1 (16%)	5 (84%)	0	0	2
<i>C. Recurrent adnexitis</i>							
Mild	13	Pall.	3 (23%)	8 (61%)	2 (16%)	0	3
	29	Chemo.	15 (52%)	12 (41%)	2 (7%)	0	1
Moderate	14	Pall.	0	14 (100%)	0	0	12
	48	Chemo.	7 (15%)	41 (85%)	0	0	14
Severe	10	Pall.	0	10 (100%)	0	0	8
	20	Chemo.	0	20 (100%)	0	0	9

*Pall., Palliation.

†Chemo., Chemotherapy.

‡Lap., Laparotomy.

longer period of hospitalization were classified as moderate. The patients who were found to have tuboovarian abscess or pyosalpinx, evidence of peritonitis or parametritis, and a prolonged febrile reaction were included in the severe group (Table III).

It is extremely difficult to evaluate clinically, actual differences in the rate of improvement between the different groups of cases. Practically every case of adnexal disease varies in its temperature response, its effect on erythrocyte sedimentation rate, duration of tenderness and even the rapidity with which the adnexal masses decrease in size or completely disappear. In order to overcome any error in interpreting the degree of improvement following any specific course of treatment, it was considered advisable to judge each group according to a specific physical standard, depending on whether complete resolution of adnexal masses did or did not occur, or on whether palpable adnexal pathology, absent on the patient's admission to the hospital, developed during the period of treatment.

The patients with mild primary acute salpingitis of less than five days' duration, responded well to chemotherapy. Complete resolution of adnexal masses occurred in 70 per cent following one week of therapy with either sulfanilamide or sulfathiazole, whereas complete resolution occurred in only 20 per cent of the control group treated with palliation alone. Sixty-six per cent of the moderate group of primary adnexal disease under five days' duration responded with complete resolution of palpable adnexal pathology following chemotherapy.

The results of chemotherapy were less striking when more than five days elapsed before the onset of sulfonamide therapy in those patients

TABLE IV. EFFECT OF CHEMOTHERAPY ON ACUTE ADNEAXAL DISEASE

TYPE	R	AV. HOSP. STAY	AV. DURATION OF TEMP. DAYS	AV. DURATION OF TENDERNESS DAYS	AV. PERIOD OF RAPID E.S.R. DAYS
<i>A. Acute primary adnexitis, less than 5 days' duration</i>					
Mild	Pall.	10.4	3.4	10	—
	Chemo.	11.9	1	7.5	—
Moderate	Pall.	—	—	—	—
	Chemo.	26.5	4.3	8	—
Severe	Pall.	—	—	—	—
	Chemo.	21	6	7	—
<i>B. Acute primary adnexitis, over 5 days' duration</i>					
Mild	Pall.	10	Less 1	7	—
	Chemo.	14.5	1	7.5	—
Moderate	Pall.	—	—	—	—
	Chemo.	23	4.5	8	—
Severe	Pall.	43	21	43	—
	Chemo.	34	5	12.5	—
<i>C. Recurrent adnexitis</i>					
Mild	Pall.	20	2	12	5
	Chemo.	14	Less 1	8	1
Moderate	Pall.	37	4	19	15
	Chemo.	26.5	3	10	6.5
Severe	Pall.	54	16	32	36
	Chemo.	37.5	11	18.5	25

with an initial attack of acute salpingitis. In this group, only 21 per cent showed complete disappearance of adnexal masses following chemotherapy, as compared with 33 per cent following simple palliation. The moderate and severe cases in this group showed an equally poor response to either sulfanilamide or sulfathiazole (Table III).

Mild recurrent adnexitis, in the acute phase, showed 52 per cent complete resolution of masses following chemotherapy as compared to 23 per cent following palliation. However, the moderate and severe groups showed no better response to chemotherapy.

Blood levels of the sulfonamides were estimated in a few cases, and these were found to vary between 0.8 mg. and 4 mg. per 100 c.c. of blood. The efficacy of the treatment with these drugs was found to bear no relation to the blood level and therefore no attempt was made to raise the concentration of the drug in the blood to any specific level.

The toxic reactions encountered during sulfanilamide or sulfathiazole administration were minimal. In 3 per cent of the cases slight gastric irritation was encountered. In one patient a slight leucopenia developed during the course of therapy, but this responded well to a blood transfusion.

Effect of Chemotherapy on Other Factors.—Chemotherapy failed to shorten the period of hospitalization in either primary or recurrent adnexal disease. Similarly no diminution in the period of adnexal tenderness, temperature reaction or rapid erythrocyte sedimentation rate was observed for the group treated with chemotherapy (Table IV).

Discussion

When the results of this study are analyzed, the marked contrast in the response to chemotherapy between the gonococcal lesions of the endocervix and urethra and the lesions above the internal os becomes readily apparent. Sulfanilamide and sulfathiazole have been found to be equally effective in the treatment of gonorrhea below the level of the internal os. An apparent 100 per cent cure rate for gonococcal urethritis and endocervicitis was obtained with the sulfonamides used in this study. This observation was based entirely on the reading of smears and was not corroborated by cultural methods or prolonged follow-up. If these additional measures had been employed, it is possible that some failures would have been revealed.

The response to chemotherapy of the lesions of gonococcal origin above the level of the internal os was less impressive. The effectiveness of this form of treatment was found to depend directly upon the extent of pelvic pathology, and on the duration of the disease before sulfonamide therapy was instituted. The best results were obtained in the treatment of the mild form of acute salpingitis less than five days old. Complete resolution of pelvic pathology occurred in 70 per cent of the cases in this group following chemotherapy as compared with 20 per cent following palliative treatment alone. Sixty-six per cent of the moderate cases of acute adnexal disease responded well to the sulfonamides when treatment was started less than five days from the onset of the disease (Fig. 1). Permanent tubal damage may be prevented or minimized

in many instances if chemotherapy is started within five days of the onset of the initial attack of adnexitis.

The effectiveness of chemotherapy decreased markedly in the group of acute salpingitis of more than five days' duration before the drug was administered. Only 33 per cent of the mild, 35 per cent of the moderate, and 16 per cent of the severe cases in this group showed a favorable response to sulfonamide therapy (Fig. 1). The effect of chemotherapy was equally unimpressive in the treatment of recurrent salpingitis particularly in the moderate or severe grades of the disease. Gillette,⁴ Goff,⁵ Williams¹⁰ and Goodwin⁶ confirm this conclusion that the sulfonamides are of little value in the treatment of acute adnexal disease after the inflammatory process in the tubes has become well developed.

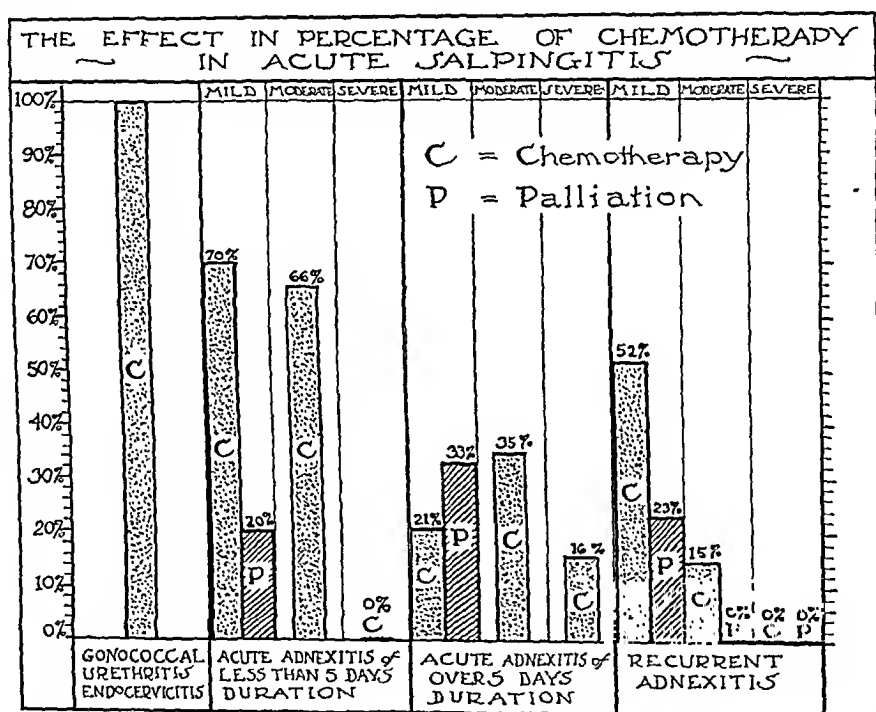


Fig. 1.—Graphic presentation of the effect of chemotherapy in acute salpingitis. Each column represents, in percentages, the favorable response obtained for the various forms of the disease from chemotherapy (C) or palliation (P).

In considering the favorable results obtained in the treatment of acute salpingitis of less than five days' duration in contrast with much less favorable response of cases of longer duration, the explanation may possibly lie in the character of the inflammatory reaction. In early acute gonorrheal salpingitis this reaction consists mainly of congestion, edema, and leucocytic infiltration of the mucosa. Large quantities of exudate are absent from the lumen, and structural alteration has not yet occurred. The effectiveness of chemotherapy in checking such a process is easily understood. In cases of longer duration, the inflammatory reaction results in extensive structural alteration of the mucosa,

in sealing the tubes usually at the ampullary or uterine extremities and the accumulation of varying amounts of exudate within the lumen. Such localized collections of exudate have been shown to contain a factor neutralizing the action of the sulfonamides.⁸ It is equally easy to understand the failure of these drugs to affect favorably the cases of advanced salpingitis.

Summary and Conclusions

1. Two hundred and four cases of acute salpingitis were studied. Of these 71 were admitted during a primary attack and 133 during an acute exacerbation of chronic salpingitis.

2. Gonococcal endocervicitis and urethritis responded well to chemotherapy. All cases of positive spreads became negative after treatment with sulfanilamide or sulfathiazole as far as could be judged by the reading of smears.

3. The effectiveness of chemotherapy in the treatment of gonorrheal lesions above the level of the internal os depends directly upon the duration of the disease before therapy is begun and upon the extent of tubal damage which has occurred.

4. Seventy per cent of the mild cases and 66 per cent of the moderate cases, with an initial attack of salpingitis of less than five days' duration showed complete resolution of adnexal masses after one week of chemotherapy.

5. Primary salpingitis of over five days' duration, and recurrent salpingitis in the moderate or severe groups, showed no adequate response to chemotherapy.

6. Permanent tubal damage may be prevented or minimized if chemotherapy is started within five days of an initial attack of adnexal disease.

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MISSED ABORTION

An Analysis of Results Following Conservative Management

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THE problem of dealing with a pregnant woman who has a dead fetus in her uterus has always been controversial. It is common experience that, when a fetus dies in utero, labor sets in within a short period of time, with expulsion of the gestational contents. However, there remains a small group of cases where the dead ovum is retained for varying lengths of time up to months and in a few cases, to years.

The paucity of reports¹⁻³ and the variation in opinion as to methods of dealing with this obstetric complication prompted us to review our experience with this clinical entity.

To define the limits of retention is difficult. Arbitrary figures are assigned by many authorities on a more or less empiric basis. Oldham,⁴ from Gny's Hospital, in 1847, was the first to mention this condition under the term of "missed labor," in which case he described the abnormal retention of a full-term dead fetus. A comparable term describing the retention of a dead fetus before viability led to the choice of "missed abortion," which was proposed by Duncan⁵ in 1878. Actually, from a theoretical standpoint, the term missed abortion should apply to retention of the full gestational contents in cases where death of the ovum occurs before the twenty-eighth week, and missed labor to those cases where death of the fetus occurs at term and retention follows. This would leave a group of cases where death of the fetus occurs from the twenty-eighth to the fortieth week, and for this group we suggest the term "missed premature labor." This would be in keeping with our accepted textbook definitions of abortion, premature labor, and labor.

What is meant by the term "retention of the dead gestational contents for an abnormal length of time?" This last phrase has led to much discussion. How long does it usually take for a woman to expel a dead fetus? Opinions expressed by various authors^{1, 6-9} regard the period of retention as anywhere from a few days to ten weeks. Theories^{1, 10, 11} as to the reasons for the spontaneous expulsion of the dead ovum include foreign body reaction, pressure against the paracervical ganglia, and endocrine imbalance.

The fate of the dead fetus depends, according to Hurd,⁷ on the period of gestation when death occurs. The early ovum may undergo complete dissolution, while older gestations may undergo mummification,

maceration, lithopedian formations, or putrefaction. The commonest change observed probably is maceration. An interesting observation relative to the proper method of therapy is the conclusion by the same author that putrefaction is not so common in missed abortion as in ordinary abortion and that so long as the amniotic sac remains intact it practically never occurs. Obviously, with the rupture of the sac, bacterial invasion by aerobic and anaerobic organisms results in cellular infiltration.

The symptoms which indicate death of the fetus vary according to the stage of development. Death of an early embryo may show no symptoms, as evidenced by spontaneous expulsion of a missed abortion in cases never suspected. In some instances women will volunteer information relative to the disappearance of the early subjective symptoms of pregnancy. On the other hand, after fetal movements have become established, their sudden disappearance, along with failure of uterine growth in proportion to the amenorrhea, bespeak cessation of fetal growth and death of the embryo. In addition, failure to experience fetal activity at the accorded date may lead one to suspect the condition. Clinically, according to Dippel,¹² the diagnosis of this condition offers little difficulty, provided that its possibility is borne in mind.

The laboratory tests which aid in the detection of fetal death are several in number. They consist of x-ray, the Aschheim-Zondek test, prolactin and estrin determination in blood and urine, urinary pregnandiol excretion and fetal electrocardiography. Most of these diagnostic aids are relatively new and are not mentioned by the earlier observers. With the utilization of the more recent diagnostic methods, earlier recognition of this condition is now possible.

The pathologic picture encountered varies in different cases. However, in order to explain the failure of expulsion of the dead ovum, it is assumed that the fetus dies either through faulty metabolism or a disturbance in its circulation, as evidenced by umbilical cord abnormality. The placenta lives longer in view of the fact that its circulation is maintained by contact with the maternal blood circulating in the intervillous spaces. This aforementioned fact accounts in many cases for the discrepancy in the size of the fetus and the size of the placenta, the latter being larger than one would expect with a corresponding size fetus. Some believe that in the cases where the primary pathology involves the placenta, the ordinary course of events observed in a threatened abortion which finally terminates in a complete abortion, is observed.

Because of the difference of opinion found in the literature as to the best method of handling these cases after the diagnosis has been established, we are presenting our experience with this condition. We analyzed 18 cases* in all where the fetus died before viability was reached and was retained for at least twenty-eight days. This one-month retention period is arbitrary, but coincides with the expression of several other investigators. In addition, we are differentiating missed abortion from missed premature labor and are not including the cases where the fetus died between viability at twenty-eight weeks and term at forty weeks.

*17 cases are from the Cumberland Hospital, Brooklyn, N. Y.
1 case is from the Prospect Heights Hospital, Brooklyn, N. Y.

Data

The ages of the patients varied between 20 and 44 years; 7 were between 20 and 30, 6 between 31 and 40, and 5 between 41 and 44. The average age was 32.5 years.

The gravidity varied between 1 and 13. The total included 1 primigravida, and 17 multigravidas, divided as follows: 2 pregnaneies 3, 3 pregnaneies 3, 4 pregnaneies 3, and from 5 to 13 pregnaneies 8. Only 1 patient had a previous missed abortion, giving an incidence of repeated missed abortion of 1 in 18, or 5.5 per cent.

In an effort to determine the incidence of previous abortions or stillbirths, we found that 7 cases, or 38.5 per cent, had previous abortions, and 6, or 33 per cent, had previous stillbirths. One case, or 5.5 per cent, had a previous cesarean section, and 2, or 11 per cent, had previous curettages for retained secundines following spontaneous abortions.

The signs and symptoms encountered in order of their relative frequency were brownish vaginal discharge in 9 cases, cessation of fetal movements in 8, mild abdominal pain in 5, failure to experience fetal activity in 4, and slight vaginal bleeding in 4 cases. Chilliness and anorexia were encountered in 1 case. One case was associated with syphilis and 2 with chronic nephritis. Elevated blood pressures over 140/90 mm. of mercury were found in 7 cases, and 5 fetal deaths were associated with toxemias. One case gave a history of pernicious vomiting in the first trimester. Foul taste, vomiting, and mental symptoms after fetal death were not observed.

The commonest clinical finding was absence of fetal heart sounds where the fetus was supposedly over twenty weeks' gestation, and a smaller sized uterus than one would naturally expect to correspond with the chronologic period of amenorrhea. In five instances the patients failed to gain weight, or showed a loss of weight with a supposedly advancing pregnancy. Observations on the disappearance of the uterine souffle and the condition of the cervix or the body of the uterus were not frequent. However, in three cases the cervix was described as firm in consistency and in two cases the body of the uterus was boggy. In several cases the fundus was merely recorded as soft.

The laboratory data showed only one case where anemia was present to a severe degree, the case being one of primary microcytic anemia, for which the patient received treatment.

X-rays of the abdomen were done in 14 cases and 7 cases were reported as showing evidence of fetal death. The diagnostic criteria were for the most part relaxation of the fetal skeleton, collapse of the skull bones, or overriding of the bones. Of the 7 cases presenting roentgenologic evidence of fetal death 2 showed living fetuses on previous examination. Of the remaining 7 cases 5 showed living fetuses, although one was much smaller than the period of amenorrhea would indicate, and 2 showed no evidence of fetal parts, although vaginal expulsion later resulted in the delivery of small, macerated fetuses.

The Friedman modification of the Aschheim-Zondek test was done on 12 patients. Of these, 5 were negative, 4 changed from positive to negative, and 3 were positive. The comparison between diagnosis of fetal death by x-ray and the Friedman test was interesting. In 10 cases study was possible. Five cases showed evidence of no fetus or fetal death and the Aschheim-Zondek test was negative. Three deaths, as indicated by roentgenologic examination, had positive Friedman tests and 2 patients had live infants by x-ray with negative Friedman tests.

Hormone studies of estrogens and pregnanediol were not performed. In one case the pH of the vaginal secretions was noted and a definite change from the acid to the alkaline was observed. About forty-eight hours before labor set in a change back to the acid side, with a pH of 4, was noted. This change from acid to alkaline with the death of the fetus might be indicative of a fall in the estrogenic titer in the blood. This experimental fact has been reported by Spielman and others,¹³ who regard this falling estrogenic titer of greater value than the Aschheim-Zondek test in determining fetal death. They believe that the Friedman test is significant only when negative. In a few cases we utilized serial roentgenograms, a technique advocated by Thoms,¹⁴ and found a closer clinical correlation by taking x-rays at twenty-four-to forty-eight-hour intervals. If no change in position of the fetus in relation to itself is noted, fetal death is considered very strongly. From a theoretical standpoint, we feel that this is a more significant method to determine if a fetus is dead, and death can be diagnosed in some cases perhaps ten days to two weeks before x-ray of the fetus would reveal the usual changes associated with death. In two cases we found changes in fetal position in spite of the fact that we had clinical evidence of fetal death, which included absence of a previously existing fetal heart and cessation of fetal movements.

The period of retention varied from four weeks to twenty-eight weeks.

Six cases were retained from four to six weeks; 4 cases were retained from 6 to 8 weeks; 2 cases from 8 to 10 weeks; 3 cases from 16 to 18 weeks; 1 case from 18 to 20 weeks; 1 case from 22 to 24 weeks; and 1 case for 28 weeks. The average period of retention was 11.25 weeks.

It is to be noted that the period of retention varied inversely with the age at which death of the fetus occurred. When fetal death took place early in pregnancy, the period of retention was longer than when it occurred later in pregnancy.

Management

No interference from below was attempted in cases where there was no bleeding and the only indication for surgical intervention was active bleeding. One case required a sponge stick removal of retained secundines after rupture of the membranes and passage of some of the gestational contents. Of the remaining 17 cases 16 passed the intact sac with the placenta and 1 ruptured the membranes and then delivered a macerated fetus. In 2 cases, retained for seventeen and twenty-eight weeks, respectively, stilbestrol tablets were given in 1 mg. doses daily for four and five days. In the first of these two cases spontaneous expulsion of the entire gestation followed, but in the other case the membranes ruptured spontaneously, after which bleeding followed and sponge stick removal of the retained secundines was necessary. The remaining 16 cases were followed in our Prenatal Clinic after the diagnosis was made and were treated symptomatically. In some instances medical induction of labor, using castor oil and hot enemas, was attempted without success. Surgical procedures were not attempted.

Following a recent report¹⁵ on the induction of vaginal bleeding with prostigmine methylsulfate in cases where delayed menstruation was not due to pregnancy, we gave two patients three injections of 2 e.c. each of prostigmine 1/2000 intramuscularly for three days and noted no effects. The two cases referred to above were given small doses of oral stilbestrol with good results.

The length of labor was recorded in 15 cases and ranged from three and one-half hours to forty-eight hours, the average being 11.6 hours. Only five cases lasted longer than eleven hours.

The blood loss was average or less in 16 cases and slightly more than average in only 2 cases, one of which was given stilbestrol and required operative removal of retained placental fragments. Neither of the latter two cases required transfusion.

Using the American College of Surgeons' standard of morbidity, only one case, or 5.5 per cent, showed any morbidity. This case required manual removal of the placenta following spontaneous expulsion of a dead fetus which had been retained for thirty-four days. This patient had a previous cesarean section, which might be etiologically related to the placental retention.

There were no maternal deaths in this series of 18 cases.

The average hospital stay postabortal, or postoperative, was nine days, the shortest being five days, and the longest thirteen days.

Discussion

At the present time there still exists a difference of opinion as to the best method of treatment for a woman who has a retained dead ovum. Some advocate immediate emptying of the uterus when the diagnosis is made, while others advise waiting a reasonable period of time before attempting delivery. In many cases this so-called "reasonable length of time" is not defined in limitation. Those who advocate immediate emptying of the uterus do so because of fear of the development of hemorrhage, infection, or toxemia. We have not encountered any of these potential dangers in following a waiting policy.

Theoretically, the surgical evacuation of the uterus in cases of missed abortion appears to be physiologically unsound. The hard, closed cervix encountered in these cases does not lend itself readily to dilatation as does the normal pregnant cervix. In addition, the uterine wall is usually thin and readily perforated, and the musculature is not responsive to the ordinary oxytocic drugs, such as quinine, ergot, or pituitrin. Therefore, the physiologic requirements which are necessary to expel the products of conception in missed abortion are evidently lacking. In view of this, it would seem justifiable to await nature's correction of the altered physiology, rather than to attempt interference by a method which is incompatible with sound physiologic principles.

The refractoriness of the uterus to stimulation by pituitrin and other oxytocic drugs may be explained by the extremely low level of blood estrin present in these cases. A few observers have attempted priming of the uterus with estrogenic hormone or stilbestrol and then utilizing pituitrin to induce emptying. Jeffcoate¹⁶ reports a high percentage of success with this form of therapy. Recently, Bickers and others,¹⁷ by placing a balloon in the uterine cavity in a case of missed abortion, showed an absence of the normal uterine motility which is generally present. Pituitrin failed to induce contractions. However, after priming the uterus with estrogens, an irritability was demonstrated graph-

ially and pituitrin at this time was effectual in producing evacuation of the retained contents. In cases where estrogen priming, followed by pituitrin, fails to produce uterine emptying, we believe there probably exists a disturbance of the steroids or in the receptivity of the end-organs, or perhaps the dosage is inadequate to provoke uterine motility. In the normal metabolism of steroids progesterone is necessary for the conversion of the natural estradiol to estrone and then to estriol. In refractory cases progesterone therapy is suggested concomitantly with estrogens. In cases which terminate in spontaneous expulsion, a readjustment probably takes place in the sex hormone metabolism and the patients go into labor spontaneously.

The theoretical difficulties which might be encountered in surgical evacuation of the uterus, namely, forcible tearing of a nondilatable cervix and bleeding from a noncontractile uterus, can be averted by not resorting to interference from below. The awaiting of the spontaneous onset of labor is, we believe, the better method of approach since at that time the uterine tonus is restored and contractions under the influence of oxytocies prevent excessive bleeding. The hormonal method of induction is not untimely and may be attempted with estrogens first, to be followed later by pituitrin. Some patients will go into labor with the estrogens alone. If this fails, perhaps progesterone can be utilized along with the estrogens. In addition, in spontaneous expulsion the entire ovum is generally expelled, whereas when surgical procedures are resorted to, the fragments of the gestational contents are torn away piecemeal.

Summary

A series of 18 cases of missed abortion is presented where the dead ovum was retained for at least twenty-eight days and up to one hundred and ninety-six days.

No patient, in the series reported, presented alarming symptoms of retention, as toxemia, hemorrhage, or infection.

Conservative management was employed.

There was no maternal mortality and in only one case was there any morbidity.

The Friedman test was of value only when negative.

Roentgenologic evidence of fetal death did not coincide with the Friedman test in more than 50 per cent of the cases.

The period of retention varied inversely with the stage of the gestation at which death of the ovum occurred.

Surgical and hormonal induction of labor is discussed along with the pertinent physiology.

Conclusions

Analysis of the series of cases presented justifies a policy of waiting for spontaneous expulsion of the dead ovum in missed abortion. Medi-

cal or hormonal trials to induce uterine contractions for the expulsion of the dead ovum may be attempted with safety. The term "missed premature labor" is suggested to include the cases where fetal death occurs between the twenty-eighth and fortieth week and the gestational contents are retained for more than twenty-eight days.

The authors wish to express their appreciation to Dr. William C. Meagher for his helpful suggestions in the preparation of this report.

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847 PARK PLACE
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Hardy, Grace Campbell: *Vaginal Flora in Children*, *Am. J. Dis. Child.* 62: 939, 1941.

This report consists chiefly in a record of data on smears and cultures and clinical status of 16 premature infants, of unselected 81 children in the Babies Hospital, and 93 children seen in the Vanderbilt Clinic for vaginal discharge.

In the final summary among others the following statements appear: In a study of the etiology of vaginal infections the only bacteria which could be incriminated were the gonococcus, the Group A streptococcus, and the diplobacillus of Petit. In the case of the two last organisms, there is bacteriologic and/or clinical evidence of an interrelation between infections of the upper respiratory tract and those of the genitals.

This series included more cases of proved streptococcic than gonococcic infection, but many of them being chronic, no opinion can be offered as to the original etiologic agent.

Further studies of the diplobacillus, superficially likely to be confused with the gonococcus, are indicated. Gonorrhea should not be diagnosed without complete cultural studies.

The large number of purulent discharges found in the children in the hospital wards suggests that such a reaction may be a concomitant of various illnesses and constitutional states.

HUGO EHRENFEST

TABLE II. ECLAMPSIA

	AGE	COLOR	NO. OF PREGNANCIES	PREGNANCIES IN WHICH ATTACK OCCURRED	BLOOD PRESSURE (HIGH)	URINE ALBUMIN	EDEMA	SEROLOGY
1	24	B.	5	1-4-5	200/130	+++	+	0
2	23	B.	3	3	190/100	++	+	0
3	24	B.	3	3	170/120	+	+	0
4	18	B.	2	2	180/100	++	+	0
5	22	B.	5	5	170/100	+	+	+
6	20	W.	1	1	140/90	++	+	0
7	15	B.	1	1	196/110	++	0	0
8	25	B.	6	6	210/130	++	+	0
9	17	B.	1	1	180/110	+	+	+
10	22	W.	1	1	176/110	+++	+	0
11	24	W.	1	1	160/95	++	0	0
12	18	B.	3	3	190/110	+++	+	0
13	19	B.	2	1	154/102	++	+	0
14	41	B.	9	9	212/134	++++	+	0
15	36	W.	2	1	160/100	+	+	0
16	18	W.	1	1	200/110	+++	+	0
17	19	W.	1	1	175/110	+	+	0
18	32	B.	12	9	190/140	0	0	0
19	32	B.	3	3	138/106	+++	+	0
20	25	B.	6	2	210/115	0	0	0

TABLE III

TIME AFTER DELIVERY IN WHICH E. E. G. RECORDED	NUMBER OF CASES	
	ECLAMPSIA	PRE-ECLAMPSIA
1 week	2 (10%)	6 (30%)
2 weeks	3 (15%)	4 (20%)
6 months	1 (5%)	0
1 year	6 (30%)	4 (20%)
2 years	5 (25%)	6 (30%)
3 years	1 (5%)	0
5 years	2 (10%)	0
Total	20 (100%)	20 (100%)

Electroencephalographic tracings were recorded on each patient from one week to five years after the attack of the toxemia for which they had been in the hospital. These data are recorded in Table III. It is to be noted that 75 per cent of the tracings of the eclamptics (15 patients) were taken from six months to five years following the attack, while in the pre-eclamptic group 50 per cent of the tracings (10 patients) were taken from one to two years after the attack. The intervals are adequate in most, if not in all instances, to exclude postconvulsive changes as a cause for the abnormal tracings. In this respect it is interesting that of the 10 tracings recorded in the pre-eclamptics within two weeks after delivery, only 2 revealed abnormalities. These findings were of aid in ruling out any obvious cerebral dysrhythmias which may have arisen from the pregnancy and parturition. The electroencephalographic technique consisted of six lead monopolar recordings, using the lobe of the ear as a reference point. The leads were taken from the frontal, parietal, and occipital regions. Short periods of hyperventilation were included in each record. From the scalp electrodes the potentials were led off to Grass amplifiers and recorded on a three channel

Further work has revealed that the cerebral dysrhythmia may be an inherited characteristic. It has long been suspected that the hereditary factor in epilepsy is a strong one. Roughly, seizures are five and one-half times more frequent among the near relative of an epileptic patient than among the general population. Lennox, Gibbs, and Gibbs⁵ made electroencephalographic tracings on 46 parents of epileptic patients. In 28 per cent of these families the records of both parents were abnormal, while in 94 per cent the record of at least one parent was abnormal (Fig. 3). The study indicated that even when a patient gives a negative family history of epilepsy one or both parents may have a cerebral dysrhythmia. These authors concluded that the cerebral dysrhythmia associated with epilepsy is inherited and the parent of the patient who shows such a cerebral dysrhythmia is the carrier.

With the above remarks to serve as a guide we can proceed to the work we wish to report.

Material and Methods

Forty unselected patients, 20 of whom had eclampsia, and 20 pre-eclampsia, were included in this study. With the exception of 4 patients (3 eclamptics and 1 pre-eclamptic), all had been admitted to the obstetric service of the Cincinnati General Hospital during the past five years. Each patient met the requirements recently given by Dieckmann¹ for the diagnosis of eclampsia and pre-eclampsia. The symptoms which included hypertension, edema, albuminuria, or convulsions have been summarized in Tables I and II.

TABLE I. PRE-ECLAMPSIA

	AGE	COLOR	NO. OF PREGNANCIES	PREGNANCIES IN WHICH ATTACK OCCURRED	BLOOD PRESSURE (HIGH)	URINE ALBUMIN	EDEMA	SEROLOGY
1	24	B.	2	2	190/110	+	0	0
2	23	B.	5	5	200/120	++	+	0
3	35	B.	6	6	225/115	++	+	0
4	32	W.	2	2	170/100	++	+	0
5	32	W.	6	6	174/110	0	0	0
6	42	B.	15	14-15	214/120	+	+	0
7	36	B.	8	8	150/90	0	+	0
8	27	W.	4	4	190/115	+	+	0
9	24	B.	1	1	164/100	++	+	0
10	38	W.	6	6	240/132	++	+	0
11	17	W.	2	2	158/115	++	+	0
12	30	B.	5	5	168/110	0	0	+
13	32	W.	5	5	154/90	0	+	0
14	43	W.	12	12	148/92	+	+	0
15	23	B.	2	2	150/102	0	+	+
16	16	B.	1	1	184/104	+	0	0
17	16	B.	1	1	160/110	+	0	0
18	31	W.	2	1	220/140	+++	+	0
19	42	W.	10	10	235/117	++	+	0
20	16	B.	1	1	160/130	+	+	0

A thorough history was obtained on each patient by one of us to emphasize the following points: (1) history of previous convulsions, (2) history of convulsive disorders in the family (including eclampsia), and (3) history of convulsions following the toxemia.

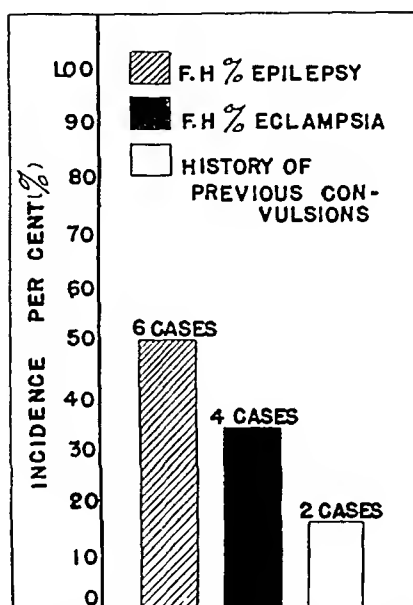


Fig. 5.—An analysis of the 12 cases of eclampsia with a history of convulsive disorders. In 6 cases there was a family history of epilepsy, in 4 cases a family history of eclampsia, and in 2 cases a history of previous convulsive episodes in the patient.

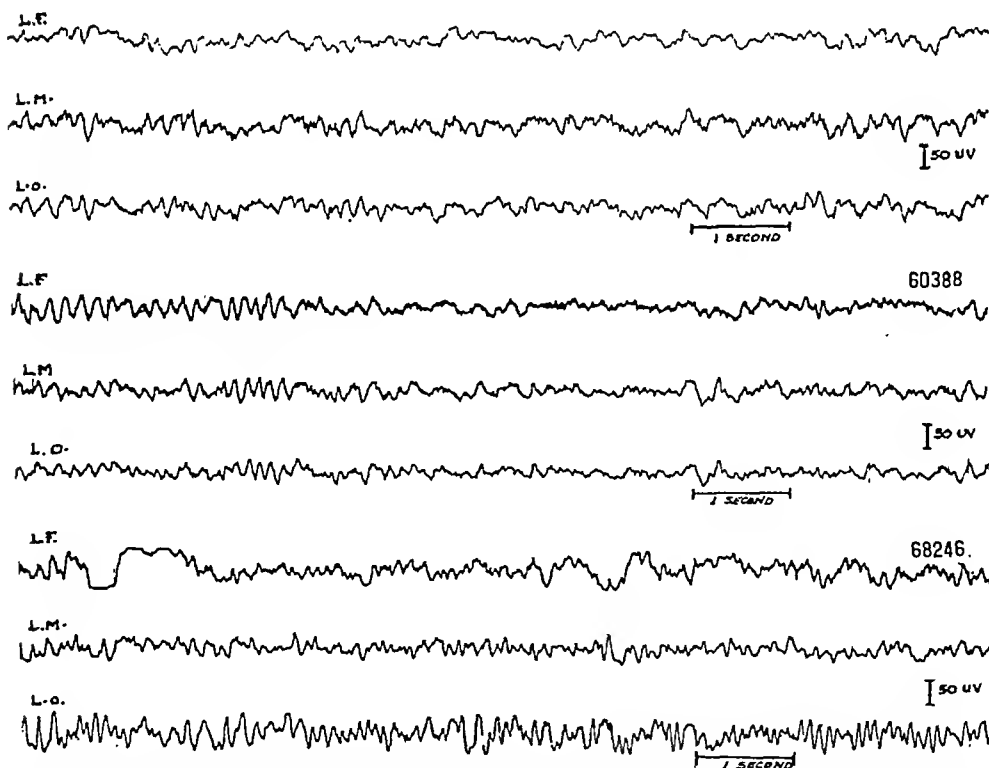


Fig. 6.—The electroencephalogram tracings in three eclamptics recorded from the left frontal, motor, and occipital areas. These recordings were made during the resting stage. Note obvious scattered slow waves, many of high voltage, and general appearance of instability in all three records.

ink writer. The records were analyzed using the standards suggested by Gibbs, Jasper, Davis,⁶ and more recently by Williams;⁶ which include frequency, amplitude, wave form, and general stability. The tracings were interpreted by one of us (G. M.) without knowledge of the patient's obstetric diagnosis and history.

Results

The results of this study are graphically depicted in Figs. 4 and 5. Thirteen of the 20 patients with eclampsia (65 per cent) had abnormalities (cerebral dysrhythmias) in their electroencephalograms, while only 2 (10 per cent) of the pre-eclamptics had similar abnormalities (Fig. 4). The abnormalities encountered (Figs. 6 and 7) were for the most part similar to those seen in the convulsive disorders (epilepsy), in that they revealed dysrhythmias characterized by slow waves with increased voltage.

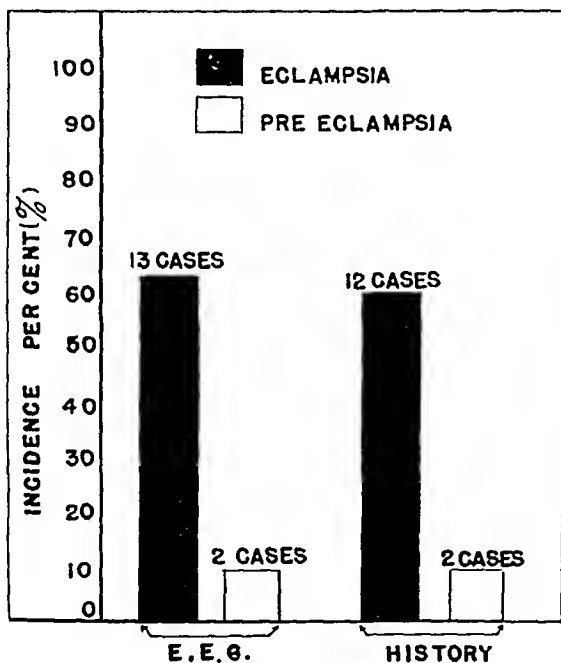


Fig. 4.—The incidence of abnormal electroencephalograms and family history of convulsive disorders in 20 eclamptics and 20 pre-eclamptics.

The historic data revealed that a convulsive diathesis existed in 12 (60 per cent) of eclamptics as contrasted to 2 (10 per cent) of the pre-eclamptics (Fig. 4). The data on the eclamptic group have been analyzed in Fig. 5. Six of the patients gave a history of epilepsy on one or more members of the immediate family. In 4 additional patients the convulsive history was limited to an attack of eclampsia in one member of the immediate family. One of these 4 patients developed eclampsia in the first pregnancy and since then has had frequent grand mal attacks (epilepsy) and is responding well to dilantin therapy. The remaining 2 patients gave a history of convulsive episodes previous to the attack of eclampsia. One of these patients had an interesting history, in that as a child she suffered from petit mal episodes and in adolescence there was an occasional grand mal attack. In her first pregnancy she

developed toxemia and during the eighth month went into severe "status epilepticus." Following recovery the patient developed more frequent grand mal attacks which recently have been controlled by dilantin therapy (Fig. 7).

A few comments regarding the data in Tables I and II may be of some interest. Of the 20 eclamptics, 14 were Negroes and 6 were white, while 11 of the pre-eclamptics were Negroes and 9 were white. These figures probably reflect the incidence of whites and Negroes on the obstetric service. The average age of the eclamptics was 24 years as compared to 29 years for the pre-eclamptics. Ten (50 per cent) of the eclamptics had the attacks in the first pregnancy while only 5 (20 per cent) of the pre-eclamptics were stricken in the first pregnancy. Also there were 7 eclamptic primiparas as compared to 4 pre-eclamptic primiparas. The above data regarding the age incidence and increased proportion of primiparas with eclampsia are in agreement with the findings of other authors.¹

Discussion

In recent years it has been demonstrated that patients suffering from convulsive disorders both in the form of "idiopathic" and "symptomatic" epilepsy have more or less characteristic types of abnormalities in their electroencephalograms. Lennox has coined the term "cerebral dysrhythmia" to indicate such abnormalities.⁴ The excellent studies of Lennox, Gibbs, and Gibbs; Robinson; and Lowenbach⁵ revealed that the cerebral dysrhythmia is an inherited characteristic, and it is this factor which predisposes one to the convulsive disorders. Although only 0.5 per cent of the general population suffer from clinical "epilepsy," it has been estimated in preliminary sampling by Lennox, Gibbs, and Gibbs⁵ that approximately 10 per cent of normal persons exhibit abnormalities similar to those seen in patients with seizures or related conditions. These "asymptomatic dysrhythmie" individuals may, of course, go through life without developing convulsive phenomena. On the other hand, in the face of conditions which affect the central nervous system either by structural changes (brain tumors, trauma, encephalitis, syphilis, etc.) or by metabolic or physiopathologic changes (drugs, toxins, changes in blood chemistry, etc.) a predisposed person is more prone to develop convulsions.⁴

Rosenbaum, Lewis, Piker, and Goldman⁷ noted that 9 per cent of a large series of patients with delirium tremens developed convulsions, and they concluded that one of the basic etiologic factors responsible for the convulsion was the underlying predisposition in the form of an inherent cerebral dysrhythmia. Recently Foster⁸ studied the association between convulsive seizures and rheumatic heart disease. He noted that the familial incidence of convulsive seizures or migraine appears in cases with rheumatic heart disease associated with seizures six times as frequently as in cases of rheumatic heart disease without seizures.

The high incidence (65 per cent) of cerebral dysrhythmias together with the high incidence (60 per cent) of positive family histories of

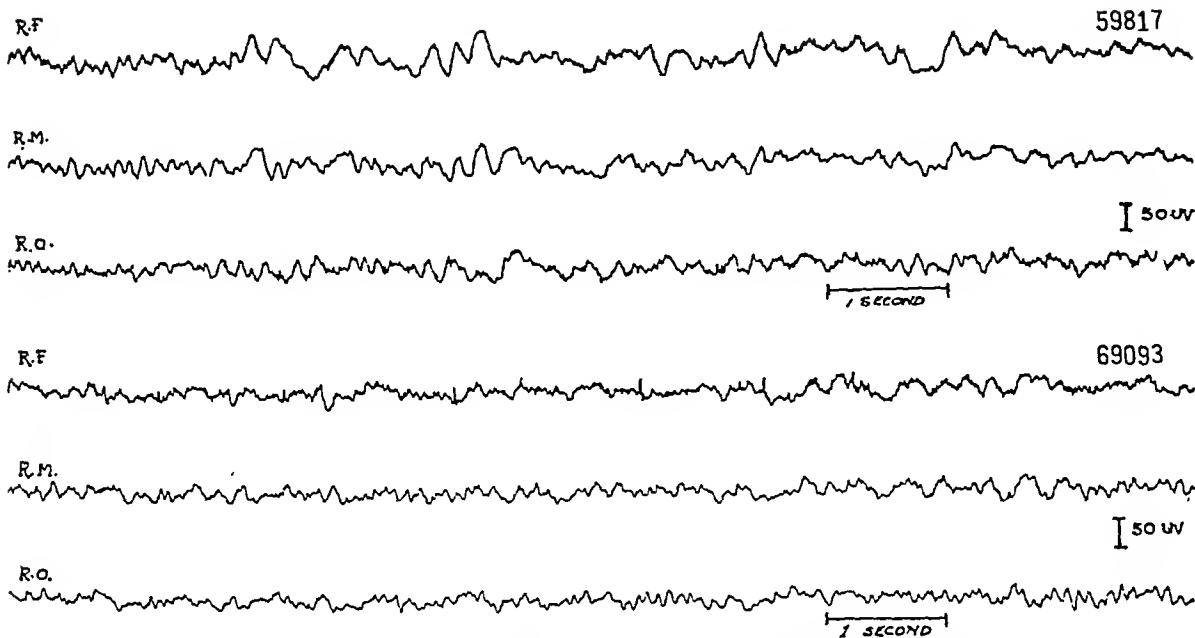


Fig. 7.—Electroencephalogram tracings on the two eclamptics with a history of previous convulsions. Recording made during the resting stage. Note marked abnormalities consisting of diffuse high voltage slow waves.

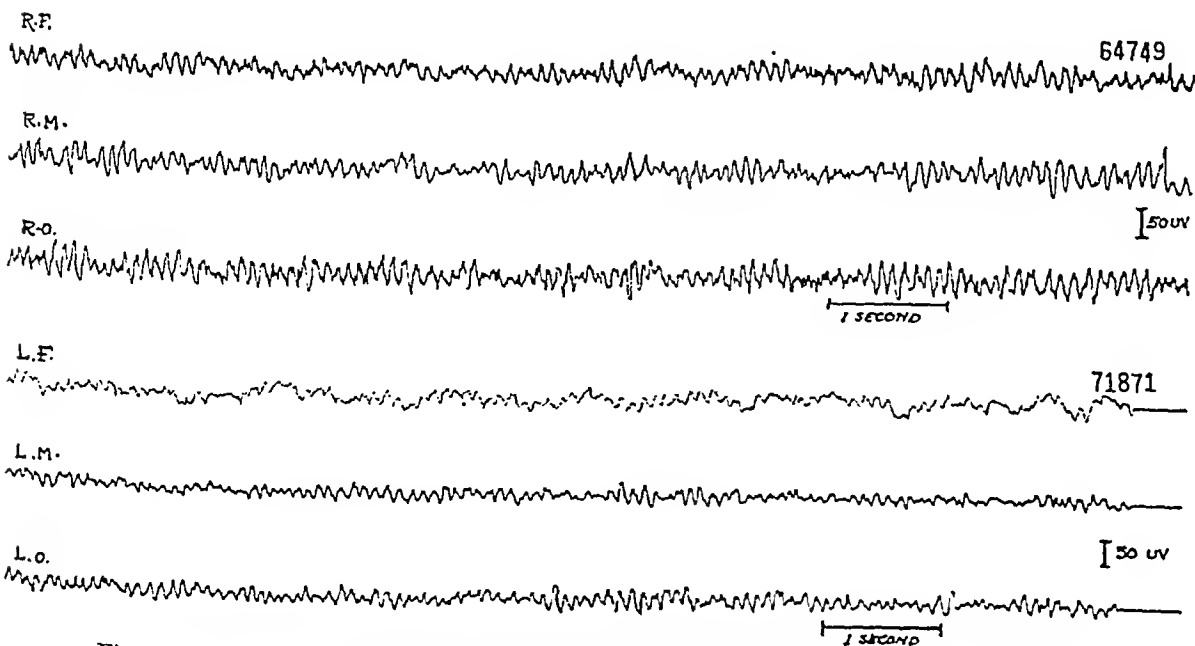


Fig. 8.—Normal electroencephalograms on two pre-eclamptics. These show a stable 10 per second rhythm of normal voltage.

per cent of the true toxemias of pregnancy developed convulsions (eclampsia). These figures are suggestive in view of the data presented by Lennox, Gibbs, and Gibbs⁵ to the effect that about 10 per cent of the normal population is predisposed toward convulsive disorders.

This study strongly suggests that a person who is predisposed toward convulsions, as evidenced by an inherent cerebral dysrhythmia, or a family or personal history of convulsive disorders, is likely to exhibit convulsions in the presence of toxemia of pregnancy. In the past this syndrome has been termed eclampsia. These studies are not concerned in any regard to the etiology of the toxemia. In accord with this concept is the fact that many of the methods that have been successful in the therapy of eclampsia have depended upon the use of anti-convulsant drugs (magnesium sulfate, sedatives, etc.).

This study may also help explain the well-known fact that eclampsia is more common in young primiparas and is more likely to occur in the first pregnancy. If during their first pregnancy a certain number of women developed a toxemia those with a cerebral dysrhythmia would be more likely to develop eclampsia in a sort of a screening out process. This would result in a relatively large percentage of eclamptics in primiparas. Another reason for a higher percentage of eclamptic attacks in the first pregnancy is that a patient who has experienced an attack of eclampsia might refrain from further pregnancies or might receive better prenatal care in subsequent pregnancies.

It may be inferred that a careful history together with an electroencephalogram may be of great importance in determining who may develop eclampsia. Furthermore, it is apparent that the proper prophylactic therapy of these people might include measures generally employed in the treatment of cerebral dysrhythmias (anticonvulsant drugs). Studies are now in progress to elucidate the action of dilantin and other anticonvulsant drugs in the pre-eclamptic and eclamptic states.

Summary and Conclusions

1. Sixty-five per cent (13 cases) of 20 patients with eclampsia had electroencephalograms indicative of cerebral dysrhythmia as contrasted to 10 per cent (2 cases) of 20 patients with pre-eclampsia.

2. Sixty per cent (12 cases) of eclamptics had a family and personal history of convulsive disorders, while only 10 per cent (2 cases) of the pre-eclamptics had a similar history.

3. It has been suggested that there may be a primary cerebral dysrhythmia present in those patients having the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear.

convulsive disorders found in this group of 20 eclamptics is striking. These findings strongly suggest that there may be a primary cerebral dysrhythmia present in patients with the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear. Signs of cerebral involvement have been noted pathologically and of course clinically. Minute hemorrhages are frequent, edema and congestion are common, and occasionally gross cerebral hemorrhages have been found in patients dying from toxemia. The convulsions have been considered to be dependent on the cerebral anoxemia resulting from cerebral vasoconstriction and/or edema.¹ These histopathologic and physiopathologic changes would thus constitute the cerebral "insult" or "trigger mechanism."

There is a paucity of material in the literature concerning the family history of convulsive disorders in eclampsia. Apparently most authors have limited the historic data to the question of a family history of eclampsia alone. Various citations have been made regarding isolated cases in which there was family history of eclampsia. In the present study, 4 of the eclamptic patients had such a history. However, the more detailed historic data gathered in this series points to a rather high incidence of convulsions (60 per cent) in the eclamptic group, and further emphasizes the important role of a "constitutional" predisposition toward convulsions in eclampsia.

Patients with epilepsy do not as a rule have more seizures during pregnancy.⁹ However, if a patient with epilepsy develops a toxemia it may be a different story. The case cited previously is pertinent. In childhood there had been petit mal attacks, and an occasional grand mal attack had occurred during adolescence. In the eighth month of her first pregnancy she developed toxemia and "status epilepticus." Patients have developed "idiopathic epilepsy" following an attack of eclampsia, and this course was experienced by one of the eclamptics considered previously in this study. Dexter and Weiss¹⁰ reported a patient with a negative personal history who developed grand mal seizures following eclampsia. A similar case was noted by DeLee.¹¹ It might be argued that such patients should not be considered as true eclamptics, but rather as having "epileptic" convulsions associated with toxemia. In our opinion the underlying factor partially responsible for the convulsion, the inherent cerebral dysrhythmia, is the same in both instances, and whether or not the patient had had clinical convulsions previous to the toxemia is of little importance.

Dieckmann¹ has presented statistical data on the incidence of the various types of toxemias in 1,100 toxemic patients. If consideration is limited to those toxemias peculiar to pregnancy (pre-eclampsia and eclampsia) only, it may be noted that 47 per cent of the patients had pre-eclampsia and 4.4 per cent of the patients had eclampsia. Thus 10

DR. DIECKMANN.—We do not.

DR. ROSENBAUM (closing).—Dr. Malthby answered Dr. Dieckmann's question in part. I was also impressed by the fact that a patient might have eclampsia in one pregnancy and never have a subsequent attack. If they do not have toxemia they will not have an attack. A patient may have eclampsia in the first pregnancy, then be all right in the second and third pregnancies, but in the fourth develop toxemia and may have another attack of eclampsia. The thing that fits into this is that there are more patients who develop eclampsia in the first pregnancy. As I went over these data I was impressed by the fact that more patients have toxemia than have eclampsia.

Some may raise the question, if a patient has eclampsia and rather serious brain changes, maybe the brain changes account for these abnormal records. That is possible. One thing I can say is that conditions which produce convulsions may produce brain damage and subsequent abnormalities in the electrocardiogram.

However, in patients treated with electric shock convulsions, the brain waves return to normal in from a few days to several months. Therefore convulsions per se are not responsible for the abnormal brain waves.

All this work has been done in the field of convulsions; we know nothing about the toxemia of pregnancy.

BREECH PRESENTATIONS TREATED BY CEPHALIC VERSIONS IN THE CONSECUTIVE DELIVERIES OF 1,700 WOMEN*

GEORGE H. RYDER, M.D., NEW YORK, N. Y.

BREECH deliveries have always been accompanied by an unduly high fetal mortality. This, as quoted by different observers, varies from a corrected mortality of about 8 per cent to a gross mortality of about 30 per cent. Most observers, however, give only the gross mortality.†

Every breech presentation, therefore, constitutes a potential danger to the fetus and breech presentations occur in 3 to 4 per cent of all term and more frequently in premature labors. The fetal mortality in vertex

*Presented at a meeting of the New York Obstetrical Society, November 10, 1942.

†De Lee¹ quotes a fetal mortality in breech deliveries of from 6 to 10 per cent; Beck² of about 10 per cent; Eden and Holland³ of 10 per cent; Curtis⁴ gives that in the University Hospital of Chicago as 13 per cent and that in the Philadelphia Lying-in Hospital as 10.4 per cent. Kerr⁵ puts it at 20 to 30 per cent and says it is consistently 8 to 10 times that of vertex deliveries. Cameron⁶ says that in the Glasgow Maternity Hospital, stillbirths among both primiparas and multiparas in breech deliveries amounted to practically 30 per cent. Edgar,⁷ in 1905, gives an average fetal mortality of 20 per cent; Williams,⁸ in 1917, quotes one of between 10 and 14 per cent; Stander,⁹ in 1941, gives the mortality as from 10 to 33 per cent and quotes Studdiford and Caldwell as giving a gross mortality of 8.3 per cent for primiparas and of 20 per cent for multiparas, with a total of 14 per cent. He gives the combined fetal mortality in the New York Lying-in Hospital for breech deliveries as 13.1 per cent. Cragin,¹⁰ in 1916, reported the total fetal mortality in breech deliveries in the Sloane Hospital for Women as 36 per cent with a mortality from dystocia of 5.7 per cent. Irving and Goethals¹¹ in their review of the deliveries at the Boston Lying-in Hospital, over a period of fourteen years, found a fetal mortality of 9.7 per cent in all breech cases, in primiparas of 12.7 per cent and in multiparas of 7.8 per cent. Mohler¹² in an article published in 1932 determined a fetal mortality of 35.4 per cent in a total number of 170 breech deliveries of over four and one-half months' gestation and gives a corrected mortality of 7.6 per cent.

4. A careful history together with an electroencephalogram might be of aid in predicting what patients may develop eclampsia.

5. The prophylactic therapy of eclampsia may include anticonvulsant drugs.

We are grateful for the cooperation of the Department of Obstetrics of the Cincinnati General Hospital.

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Discussion

DR. W. J. DIECKMANN.—This work of Drs. Rosenbaum and Maltby opens up an interesting new field in the study of toxemia of pregnancy. Their series of cases is small, as they state, so their findings are rather characteristic. Their findings of potential convulsions may explain why some of our patients may have been prevented from having fits that may not have been convulsive.

One point I would like to ask is why the eclamptic patient, if she has this convulsive tendency, does not repeat in a subsequent pregnancy. It has been well established that many of them go through subsequent pregnancies without eclampsia. I have never seen a patient having eclampsia in two pregnancies, both of which were under our observation. We have had histories of such occurrence but never had them occur under our observation. It may enable us to pick up the potential eclamptics and to study them more carefully during the pregnancy. If it is possible to do that it will certainly lessen the cost of prenatal care which is becoming quite prohibitive.

One other thing that I think seems to fit is that I understood the essayists to say that, granting the series is small, they found a high percentage of eclamptics. That has not been our experience.

DR. GEORGE L. MALTBY, CINCINNATI, OHIO.—In regard to the question, why does not the eclamptic repeat the eclampsia in the second pregnancy, I would like to ask whether obstetricians do not give some different type of therapy to the patient having once had eclampsia or watch the patient more closely, give them barbiturates or something similar.

THE TREATMENT OF ACUTE INFLAMMATORY PELVIC MASSES OF TUBAL ORIGIN BY IONTOPHORESIS WITH ACETYL BETA METHYL CHOLINE CHLORIDE*

With a Report of 94 Cases

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WE WISH to present our results in treating one type of pelvic inflammation, using acetyl beta methyl choline chloride† by iontophoresis.

The pharmacology and technique employed in administering the drug by this method has been described by Jacoby.¹

Material

From April 1, 1938, to Jan. 1, 1941, there were 2,087 admissions to the gynecologic service of the Lincoln Hospital. Of these, 416 (20 per cent) had inflammatory conditions of the pelvic organs. We selected 65 cases of acute pyosalpinx or acute salpingo-oophoritis with exudate and pelvic peritonitis. All inflammations of postabortal origin or parametritis arising from intra-uterine infection were excluded. Our study was restricted to one type of pathology in order to better evaluate the results. Of the 65 selected patients, 11 were eliminated because of inadequate treatment or follow-up. There remained 54 hospital patients who were adequately treated and followed. All were examined and followed by the authors.

In addition, 40 ambulatory patients were treated and followed in the out-patient department. Twenty-five per cent of these were ill enough to require hospitalization, but they refused to be admitted. In both groups, the criterion for selection was the same: an inflammatory mass of tubal origin 5 cm. or more in diameter, unilateral or bilateral. The follow-up period on each patient was terminated by an insufflation test, an operation, or subsequent pregnancy.

Factors Studied

The distribution of cases with reference to the various factors studied, viz.: color, age, parity, abortions, previous attacks, past operations, duration of pain and effect on menstruation are found in Tables I, II, and III.

Findings

Tables IV and V present both clinical and laboratory findings, when the patients were first examined. Fifty-six per cent had infections of

*Presented, by invitation, at a meeting of the New York Obstetrical Society, May 12, 1942.

†The trade name of this compound is mecholyl (Merck & Co.).

deliveries, at a conservative estimate, is about one-fifth that in breech deliveries. Thus, it may be assumed, that unborn babies changed from breech presentations to vertex presentations have a five times better chance of survival.

External cephalic version has long been recognized as a means of converting breech presentations into the much safer vertex presentations. However, it appears that this operation has not been sufficiently appreciated by obstetricians in general, probably for two reasons: (1) Ante-partum abdominal palpations are not carefully and repeatedly made, hence breech presentations are often not discovered early; and (2) the operation of external cephalic version is not attempted frequently enough for acquiring the necessary skill.

I have made a practice consistently of attempting to diagnose breech presentations as early in pregnancy as possible and of trying to convert all found to vertex presentations by cephalic versions, where practical. After performing many external cephalic versions, I am convinced that the maneuver carefully performed is practically devoid of danger to mother and child and in the majority of cases is easily accomplished.

In 1923 I¹³ published a report of 59 breech presentations treated by cephalic versions in 890 consecutive deliveries of private patients. The present report includes this former report in a series of 1,700 consecutive deliveries of private patients, showing the results of cephalic versions in breech presentations.

This paper is presented in the hope that it may stimulate interest in external cephalic version and may induce more obstetricians to adopt it as a routine practice in the ante-partum care of their patients.

Material

In this series of 1,700 women, systematic effort was made to diagnose breech presentations early and to change all found to vertex presentations by cephalic versions where feasible, with the object of having as few breech deliveries as possible. The goal set was to have no breech deliveries, particularly in primiparas at term with single pregnancies. This goal was not reached, but the results were very encouraging and the fetal loss from dystocia was extremely low.

TABLE I. TABULATED SUMMARY OF CASES

		BREECH PRESENTATIONS
Babies nonviable at birth	32	14, or 43.7%
Babies viable at birth	1,689	258, or 15.3%
All babies	1,721	272, or 15.8%

Incidence.—In the deliveries of the 1,700 women, 1,721 babies were born, 32 before the period of viability and 1,689 after viability (Table I).

Breech presentations in babies born before the period of viability are of little importance, presenting no problem at delivery and having no bearing on the outcome. Hence, in this paper the nonviable babies are excluded and attention is directed only to those born viable.

Among the viable babies, at some time during pregnancy, about 1 in 6 (258) were found in breech presentation. At time of birth, however, due chiefly to external cephalic versions and in much lesser degree to spontaneous versions, only about 1 in 37 (45) remained in breech presentation (Table II). And of the 45 in breech presentations at birth, 13 were premature.

TABLE II. BABIES VIABLE AT BIRTH (1,689)

	BREECH PRESENTATIONS
At some time during pregnancy	258 or 15.3%, 1 in 6
At time of birth	45 or 2.6%, 1 in 37
(Due chiefly to external cephalic versions)	

It is generally stated that the incidence of breech presentations is very high in the early months of pregnancy and that the incidence decreases greatly as term approaches. It is interesting to note that in this series, with many artificial versions, the incidence fell off very sharply as term approached. Among the nonviable it was 44 per cent, among the viable premature it was 13 per cent, and among those at term it was only 2 per cent (Table III).

TABLE III. BREECH PRESENTATIONS OF 1,721 BABIES AT BIRTH AFTER VERSIONS ARTIFICIAL AND SPONTANEOUS

		BREECH
Nonviable	32	14, or 43.7%
Viable premature	99	13, or 13.1%
At term	1,590	32, or 2.0%
	1,721	59, or 3.4%

Results Obtained by Cephalic Versions.—Of the 258 babies found in breech presentation at some time during pregnancy, over three-fourths (198) were changed by cephalic versions to vertex presentations, so remaining at birth; 5.8 per cent (15) changed spontaneously; and 17.5 per cent (45) were left as breech (Table IV).

TABLE IV. VIABLE BABIES ORIGINALLY IN BREECH PRESENTATION (258)

Changed by external cephalic versions	197
Changed by internal cephalic version	1
Total changed artificially	198, or 76.7%
Changed spontaneously breech to vertex	15, or 5.8%
Total changed artificially and spontaneously	213, or 82.5%
Remaining breech at birth	45, or 17.5%
	258 (100.0%)

Reasons Why the 45 Were Left in Breech Presentation.—The 45 left as breech represented 16 failures, partial and complete, of cephalic versions; and 29 on whom no attempt at version was made, because of twin pregnancies, incomplete observation, consultations, etc. (Table V).

TABLE V. REASONS FOR BABIES LEFT AS BREECH (45)

Partial failure of external versions (turned to vertex but reverted, so remaining)	6
Complete failure of external versions (could not be turned even once)	10
No attempt at external versions	29
	<hr/> 45

Number of Babies on Whom Cephalic Versions Were Attempted.—Among the 258 babies originally in breech presentation, 15 changed spontaneously to vertex and on 29 no attempts at versions were made. There remained 214 on all of whom attempts at version were made (Table VI).

TABLE VI. VIABLE BABIES ORIGINALLY IN BREECH PRESENTATION

Left as breech with no attempt at versions	29
Spontaneous versions to vertex	15
Cephalic versions tried on	214
	<hr/> 258

Percentages of Success and Failures at Conversions to Vertex.—Complete success was attained in 92.5 per cent of these attempts at conversion from breech to vertex, all of the 198 babies so changed being in vertex presentation at birth. There was partial failure in 2.8 per cent of the attempts, as reversions to breech occurred and all 6 babies were in breech presentation at birth. In 4.7 per cent there was complete failure, as the presentations of these 10 babies could not be changed even once (Table VII).

TABLE VII. CHANGE OF PRESENTATION BY CEPHALIC VERSION TRIED ON 214 BABIES

Complete success, vertex at birth	198, or	92.5%
Partial failure, changed but reverted, breech at birth	6, or	2.8%
Complete failure, could not be changed, breech at birth	10, or	4.7%
	<hr/> 214, or	<hr/> 100.0%

Reasons for the Six Partial Failures.—The six partial failures were equally divided among multiparas and primiparas. In the former, versions were performed at least once on each baby, but reversions recurred and discovery was made too late in labor for further attempts at version.

In the primiparas, one baby was turned to vertex in the sixth calendar month and two in the eighth month. All reverted to breech and could not be returned. The mother of the first of the three babies, due to intercurrent illness, was not seen again until the eighth month. So all these three failures occurred in the eighth month and all were due in part at least to the complication of extended legs of the fetuses.

Reasons for the Ten Complete Failures.—These ten complete failures occurred in one multipara and in nine primiparas. The reason for the

failure in the multipara was multiple fibroids. The uterine wall was so thick that diagnosis of presentation could be made by x-ray only and serious attempts at version were not persisted in.

The cause of the failures in the nine primiparas was due to the fact that all of the attempts at version were made in the eighth and ninth months of pregnancy. Contributing causes were: in six, extended legs of the fetuses and in the other three, adhesions under old abdominal scars, with a small amount of liquor amnii, and obesity with badly taken anesthetic.

It is to be noted that of the 12 failures, complete and partial, or primary and secondary, in primiparas, the complication of extended legs was present in nine or 75 per cent, while *all* failures were in the eighth or ninth months of pregnancy.

In primiparas, therefore, two factors seemed to make external versions especially difficult, extended legs of the fetuses and delay in making the attempt until late in pregnancy. When both of these factors are present, in my experience, failure is very likely to occur. In the whole series, there was no failure at conversion to vertex before the eighth month of pregnancy, whether in the presence of extended legs or not. And without this latter complication, there were many successful conversions after the eighth month (Table XV).

In multiparas, with the exception of one failure due to multiple fibroids, there was no complete failure, whether the attempt was made late or early, in the presence of extended legs or not.

All of the cephalic versions except three were performed before labor. Two external cephalic versions were performed in the first stage of labor, one in a primipara and the other in a multipara. One internal cephalic version was performed in a multipara in the second stage of labor. This is described later.

Delivery of the 258 Babies Originally in Breech Presentation

Of the babies originally in breech presentation, over three-fourths (204) were delivered vaginally as breech; about 13 per cent (33) were delivered vaginally as breech; and 8 per cent (21) were delivered by section. Slightly less than one-half (10) of the sections were performed because of the breech presentations, the others for reasons unconnected with the presentations. Of all the viable babies originally in breech presentation, 3.5 per cent were delivered by section because of persisting breech presentations, all being babies of primiparas (Table VIII).

TABLE VIII. DELIVERY OF 258 BABIES ORIGINALLY IN BREECH PRESENTATION

As vertex, vaginally		204, or	79.1%
Spontaneous	139		
By forceps	65		
As breech, vaginally		33, or	12.8%
By section		21, or	8.1%
Converted, vertex	9		
Not converted, breech	12		
(Because of breech	10)*		
(Because of fibroids	2)		
		258, or	100.0%

*Sections because of breech, 10, or 3.5%.

Reasons Why 33 Babies Were Delivered Vaginally as Breech.—The babies delivered vaginally as breech were those in twin pregnancies;

those not under observation in the latter part of pregnancy; those changing suddenly to breech presentations too late for attempts at versions; two in consultations after labor had started; and two upon whom artificial versions had failed (Table IX).

TABLE IX. BABIES BORN VAGINALLY AS BREECH. WHY SO BORN

In twin pregnancies	13
Not under complete observation	10
Spontaneous versions and reversions to breech too late for attempts at version	6
Consultations after labor started	2
Failure of cephalic versions	2
	<hr/> 33

Of the babies having breech deliveries, only six were of primiparas at term with single pregnancies (Table X). And of these six primiparas, one was never seen until well advanced in labor and three were not seen during the last weeks of pregnancy until just before labor. The remaining two had breech deliveries because of the failure of external versions (Table XI).

TABLE X. BREECH DELIVERIES

			OF PRIMIPARAS	OF MULTIPARAS
At term	{Single babies	13	6	7
	{Twins	7	4	3
Premature	{Single babies	7	3	4
	{Twins	6	3	3
33			16	17

TABLE XI. TERM BABIES OF PRIMIPARAS IN SINGLE PREGNANCIES DELIVERED AS BREECH

Not under observation before labor—consultation	1
Not under observation during last month	3
Failure of external cephalic version	2

It follows, therefore, that in the consecutive deliveries of 1,700 women, of all *under complete observation throughout pregnancy*, only two primiparas at term with single pregnancies had breech deliveries.

Fetal Mortality of Viable Babies Originally in Breech Presentation

The fetal mortality from all causes among the 258 babies originally in breech presentation was 8, or 3.1 per cent. The corrected mortality or that from dystocia only was 2, or 0.8 per cent (Table XII).

Six of the babies were lost from causes unconnected with delivery, placenta previa, accidental hemorrhage, enterocolitis, hydrocephalus and prematurity.

TABLE XII. FETAL MORTALITY OF 258 VIABLE BABIES ORIGINALLY IN BREECH PRESENTATION

From all causes	8, or 3.1%	Omitting 1 consultation	1, or 0.4%
From dystocia only	2, or 0.8%		

The two babies lost from dystoeia were of primiparous women at term in frank breech deliveries. The mother of one was first seen in consultation after more than forty-eight hours of labor, with membranes ruptured and breech impacted, delivery being possible only after craniotomy. The mother of the other baby was not seen during the last two weeks of pregnancy, due to a sinus infection.

Two babies only, then, in this series were lost from dystoeia. External version was not tried on either of them from lack of opportunity. Therefore, of all the 258 babies originally in breech presentation before labor whose mothers were under my care before labor, the loss from dystocia was one, or 0.4 per cent. And of all those whose mothers were under complete and satisfactory observation throughout pregnancy, there was no loss from dystoeia.

Moreover, among all of the babies on whom cephalic versions were attempted, successfully or unsuccessfully, not only was there no loss from dystoeia, but there was no injury. And among all those upon whom external cephalic versions were performed, just two babies were lost, one from accidental hemorrhage eight weeks after the version; and the other from prematurity seven weeks after the version. Neither loss could be attributed to the version or to dystoeia.

So it can be stated definitely that of all the fetuses upon whom cephalic versions were tried, none suffered harm; and among all changed by cephalic versions from breech to vertex, there was no loss from dystocia or from the effects of the versions. The only loss from dystocia was among those upon whom cephalic versions were not attempted.

Maternal Mortality

Among all of the women upon whose babies cephalic versions were attempted successfully or unsuccessfully, there was no mortality.

Facts Concerning External Cephalic Versions Performed

Concerning the external versions performed in this series, some facts are interesting. These versions were performed on 203 babies, with slightly over three-fourths on those of multiparas (Table XIII).

TABLE XIII. CONVERSIONS TO VERTEX BY CEPHALIC VERSIONS (204 BABIES: ENTIRELY SUCCESSFUL, 198, AND PARTLY SUCCESSFUL, 6)

By internal cephalic	1 in a multipara	
By external cephalic	203	
In multiparas	154 or	75.9%
In primiparas	49 or	24.1%
	203	100.0%

Months in Which External Versions Were Performed.—Particular attention is called to the time at which these versions were first performed. About three-fourths were in the sixth and seventh calendar months and only about one-fourth in the fifth, eighth, and ninth months (Table XIV).

External Versions With and Without Anesthesia.—No anesthesia was used in changing presentations from breech to vertex in over 95 per cent of the babies. In nine only, or in less than 5 per cent, was anesthesia used, all nine being in the eighth or ninth month at time of

TABLE XIV. TIME OF CONVERSIONS TO VERTEX BY EXTERNAL CEPHALIC VERSIONS
(203 BABIES)

In 5th calendar month	7 babies or	3.4%	—in 6th and 7th, 73.5% or 3/4
In 6th calendar month	72 babies or	35.5%	
In 7th calendar month	77 babies or	38.0%	
In 8th calendar month	36 babies or	17.7%	
In 9th calendar month	11 babies or	5.4%	
203		100.0%	

conversion. So all conversions performed before the eighth calendar months were without anesthesia. Of those performed later, about one-fifth required anesthesia (Table XV).

TABLE XV. CONVERSIONS TO VERTEX BY EXTERNAL VERSIONS AND ANESTHESIA

Without anesthesia	194 or	95.6%
With anesthesia	9 or	4.4%
		203 or 100.0%
Conversions in 8th and 9th months	47	
Without anesthesia	38	
With anesthesia	9 or 19.1%,	about 1/5.
All conversions before eighth month without anesthesia.		

Total Number of External Cephalic Versions Performed.—The total number of external versions performed on the 203 babies was 355, as in many cases several versions were performed on one baby before the presentation remained vertex. On one baby nine versions were performed and on another thirteen. All repeated versions except two were in multiparas (Table XVI).

TABLE XVI. TOTAL NUMBER OF EXTERNAL CEPHALIC VERSIONS PERFORMED ON 203 BABIES (355)

BABIES	TIMES PERFORMED	TOTAL VERSIONS	IN MULTIPARAS	IN PRIMIPARAS
139	1	139	92	47
20	2	40	36	4
22	3	66	66	0
14	4	56	56	0
4	5	20	20	0
2	6	12	12	0
1	9	9	9	0
1	13	13	13	0
203		355	304	51
Total external versions, 355				
In 154 multiparas		304		
In 49 primiparas		51		
203		355		

TABLE XVII. TOTAL EXTERNAL CEPHALIC VERSIONS ATTEMPTED (368)

In 155 multiparas	305	Successful	304	Failures	1
In 58 primiparas	63	Successful	51	Failures	12
213	368		355		13
In primiparas after 7th month, 22					
Successful	10 or 45.5%				
Failures	12 or 54.5%				

Months When Spontaneous Versions Occurred.—Spontaneous versions occurred with 15 babies, about equally divided among those of primiparas and multiparas. Two-thirds occurred in the sixth and seventh calendar months and only one-third in the later months (Table XVIII). Thus nature's time for spontaneous versions corresponded with the obstetrician's time for artificial versions, two-thirds of the former and three-fourths of the latter occurring in the sixth and seventh months.

TABLE XVIII. SPONTANEOUS VERSIONS BREECH TO VERTEX (IN MULTIPARAS, 8; IN PRIMIPARAS, 7)

In 5th calendar month	0	observed	
In 6th calendar month	3	or	20.0%
In 7th calendar month	7	or	46.7%—In 6th and 7th, 66.7% or 2/3
In 8th calendar month	3	or	20.0%
In 9th calendar month	2	or	13.3%
	15	or	100.0%

Percentage of Reversions Occurring After First External Versions.—Reversions to breech, after first external versions, occurred in about one-third of the babies; in about 10 per cent of primiparas and in about 40 per cent of multiparas. Of five babies reverting in primiparas, two were returned to vertex and three could not be returned. Of 65 reverting in multiparas, all but three were returned to vertex by one or more external versions. These three were left as breech without further attempts at version (Table XIX).

TABLE XIX. BABIES REVERTING TO BREECH AFTER FIRST EXTERNAL CEPHALIC VERSIONS ON 203

In 49 Primiparas	5	or	10.2%—about 1 in 10
In 154 Multiparas	65	or	40.2%—about 4 in 10
203	70	or	34.5%—about 1 in 3

Cord Around Neck After External Versions.—The question is often raised whether or not external cephalic versions increase the incidence of cords around fetal necks.

In this series, the incidence of cords around fetal necks was higher among the babies on whom external versions had been performed than among those on whom no versions had been performed, though in the former the complication caused no fetal loss, while in the latter it caused a slight mortality. Although this absence of fetal loss in the former is probably a fortunate coincidence, it is worthy of mention.

Among all the babies on whom external versions had been performed, the incidence of cords around necks was about 1 in 3, while among those of the whole series on whom no versions had been performed, the incidence was about 1 in 4, 31.5 per cent and 23.1 per cent, respectively (Table XX).

Incidence of Cords Around Neck Not Increased by Repeated Versions.—The incidence of cords around fetal necks did not increase with the number of versions performed. On each of 139 babies, one version only was done. Among these there were 49 with cord around the neck, an incidence of 35.2 per cent. On each of 64 babies, two or more ver-

sions were done and among these, 15 were found with cord around the neck, an incidence of 23.4 per cent. Thus repeated versions on one baby did not seem to entail additional danger from this complication.

TABLE XX. CORDS AROUND FETAL NECKS AFTER 355 EXTERNAL CEPHALIC VERSIONS ON 203 BABIES

Total number 64, or 31.5%, nearly 1 in every 3 babies. For comparison with whole number of 1,721 babies.			
	BABIES	CORDS AROUND NECKS	FETAL LOSS FROM CORDS
Versions on	203	64 or 31.5%—nearly 1 in 3	0
No versions on	1,518	351 or 23.1%—nearly 1 in 4	6 or 1.7%
	1,721	415 or 24.1%—nearly 1 in 4	6 or 1.4%

Cord Around Neck After Spontaneous Versions.—After the 15 spontaneous versions from breech to vertex, cords were found around the neck of three babies, an incidence of 20.0 per cent. While the number of cases is too small for serious consideration, yet they serve as a reminder that cords may become wound around fetal necks after spontaneous versions as well as after artificial ones.

Case Report—An Internal Cephalic Version Performed in the Second Stage of Labor

The patient was a multipara at term. The presentation had been vertex throughout pregnancy. This was verified four days before labor. The fetal head was then at the brim of the pelvis, and there was an excessive amount of liquor amnii.

Labor started spontaneously and progressed rapidly. One the first vaginal examination, the breech was found presenting high at the pelvic brim, the cervix was fully dilated, and the membranes were intact. The position was L.S.A.

The patient was put completely under ether, the membranes were ruptured, and the right hand was passed into the uterus, pushing the breech upward along the left wall of the uterus. The left hand located the fetal head through the towels and the abdomen and guided it downward on the patient's right. The head immediately appeared at the pelvic brim and the breech was felt up under the ribs.

The head was held with the right hand and the patient was allowed to come out of ether. As uterine contractions did not start, 4 minims of pituitrin were given by intermuscular injection. With the first uterine contraction, the head came down into the pelvis and spontaneous delivery followed quickly. The baby, weighing 9½ pounds was in good condition. The internal cephalic version seemed a safer procedure than the breech delivery of such a large baby.

This internal cephalic version is the only one performed by me. The operation seems to have possibilities and might be used in a primipara under favorable circumstances.

Comments

In considering this series of breech presentations among viable babies, it is noticed that the incidence is high, about 1 in 6. This is due to the

fact that all breech presentations are listed if once diagnosed, although they may have changed later to vertex. It is probable that in any large number of ante-partum examinations, findings would be similar. All observers, however, give the incidence of breech presentations at time of labor only.

At time of labor, in this series, the incidence was found to be 1 in 37, an incidence more in accord with the observations of other writers. This change from 1 in 6 to 1 in 37 is due chiefly to external cephalic versions and but slightly to spontaneous versions.

Arguments Against External Versions Answered

One argument that may be advanced is that these external versions were not necessary, as in other series with but few external versions, or none at all, the incidence of breech presentations at time of labor is only slightly higher than in this series with many external versions.

This argument is not convincing, because it is never possible to foretell which babies in breech presentation will turn spontaneously to vertex. Many will but some will not. Hence, individual babies may suffer and be left to face later breech delivery with its high mortality. It is better to rely on relative certainty than on uncertainty.

Moreover, external versions are usually easy if attempted early. In this series, there were no failures before the eighth month and anesthesia was not needed, while after the seventh month anesthesia was needed in about one-fifth of all versions performed and of all attempted in primiparas, over one-half were failures. Spontaneous versions may occur but they are more likely to occur early, judging from this series, where two-thirds occurred before the eighth month (Tables XV, XVII, and XVIII).

Thus, it does not seem wise, when breech presentations are found, to allow them to persist much beyond the seventh month, especially in primiparas. Of the 12 failures at external versions in primiparas in this series, all occurred after the seventh month, due largely to the dreaded complication of extended legs of the fetuses. It seems probable that none of these failures would have occurred, even in the presence of this complication, if all of the attempts could have been made in the sixth or seventh month of pregnancy.

Other arguments advanced against external version are: that it may cause winding of the cord around the fetal neck; that reversions to breech occur too frequently; that it may cause premature labor; and that it may cause injury to fetus or mother.

Artificial versions do at times cause winding of cords around fetal necks. But so do spontaneous ones. If there are few of the former, there will be many of the latter and vice versa. There is little reason for thinking that either entails essentially more risk of causing this com-

TABLE I

TOTAL	COLOR		AGE		PARITY	
	W	C	15-30	31-45	Nullip.	Multip.
94						
Hospital (54)	23	31	33	21	29	25
Clinic (40)	17	23	24	16	21	19

TABLE II

TOTAL	ABORTIONS		PREVIOUS ATTACKS		PAST OPERATIONS
	0	1+	0	1+	
94					
Hospital (54)	38	16	28	26	3 1 Uterine suspension 1 Unilateral salpingo-oophorectomy 1 Exploratory laparotomy, pyosalpinx, not removed
Clinic (40)	32	8	15	25	7 5 Unilateral salpingo-oophorectomies 2. Uterine suspensions

TABLE III

TOTAL	DURATION OF PAIN			EFFECT ON MENSTRUATION	
	1 wk.	2 wk.	3 wk.	NO CHANGE	Menometrorrhagia
94					
Hospital (54)	31	20	3	34	20
Clinic (40)	10	17	13	34	6

TABLE IV

TOTAL	CERVIX		UTERUS		ADNEXA			
	Norm.	Endo-cervicitis	Ant.	Retro-verted	Bilateral masses	Unilateral mass. Bilateral involvement	Unilateral mass	Size
94								
Hosp. (54)	22	32	38	16	21	23	10	5-6 cm. (33) 7-12 cm. (18) 12+ cm. (3)
Clinic (40)	19	21	32	8	5	19	16	5-6 cm. (32)* 7-12 cm. (8)

*Hospital advised and refused, 10 cases.

TABLE V

TOTAL	CERVICAL SMEAR			SEDIMENTATION RATE					TEMPERATURE ON ADMISSION TO CLINIC		
	+	?	-	24+ 15 min.	24+ 30 min.	24+ 60 min.	18-24 60 min.	0-18 60 min.	N	99-100	100-101
94											
Hospital (54)	13	7	34	9	20	19	4	2			
Clinic (40)	6	8	26	0	8	18	6	8	10	17	13

external versions were broken. Lack of haste and gentleness are essential for the safe performance of versions. I once spent an hour in performing an external version without anesthesia.

One baby only, in the series, showed symptoms causing anxiety during an attempted version. The baby had been turned part way, when auscultation disclosed the fetal heart beating very slowly. The attempt at version was given up and the fetal heart sounds returned to normal in a few minutes. One week later, fortunately, spontaneous version to vertex was found to have occurred.

Advantages of External Cephalic Version

The value of external versions is unquestionable. By it the presentation is changed from breech to vertex with assurance of a relatively safe birth in place of a far more hazardous one. Not only is there less risk of fetal loss but also of permanent fetal injury. And the mother is assured of a labor more natural and shorter.

There are other advantages of a change of presentation from breech to vertex. In the latter presentation, disproportion between the fetal head and the pelvic brim can be recognized. In primiparas, fetal heads not dipping into pelvic brims at term, give warning of dystocia later and possible need of section. Appropriate measures can then be taken to prevent trouble.

Premature labors are less likely to occur in vertex presentations than in breech presentations, judging from this series. Among all of the viable babies whose presentations had been changed artificially and spontaneously from breech to vertex, the incidence of premature labors was slightly over 4 per cent, while among the 45 left in breech presentation, the incidence was nearly 29 per cent. This seems more than a coincidence, even allowing for the fact that many twin pregnancies were among the 45, and early changing of breech presentations from breech to vertex, far from causing premature labors, may tend to prevent them. Another fact frequently noticed is that the pregnant woman is usually more comfortable with a fetus in vertex presentation, especially in the later months. In breech presentations, complaint is often made of pain from pressure of fetal heads up under the ribs and quick relief is experienced when the presentations are changed to vertex.

Weekly Examinations After Performance of External Cephalic Versions

The routine adopted by me after performing external versions, is to ask patients to report for examination weekly. If reversions to breech have occurred, the versions are repeated. This is continued until the presentations remain vertex, as they will usually do when the fetal heads settle into the pelvic brims. Except in bed patients, the several forms of abdominal binders suggested do not seem practical, as they are hard to keep in place.

plication than the other. It seems illogical, therefore, for fear of cord complications to refrain from artificial versions and to rely upon spontaneous ones.

In this series, the incidence of cord complications was only slightly higher among babies on whom external versions had been performed than among those on whom there had been none, 1 in 3 in contrast to 1 in 4 approximately (Table XX). And while cord around the neck does at times cause fetal mortality, breech deliveries result in a far higher mortality. So every fetus left in breech presentation is in much greater danger from impending breech delivery than from a possible cord complication after external version.

It is true that reversions to breech after external versions do occur frequently but the versions may be repeated as often as necessary. In this series, reversions occurred in about one-third of the babies on whom versions had been performed. They were more frequent after easy versions and less frequent after difficult ones. Versions were more difficult in primiparas and reversions were rare, about 1 in 10; while in multiparas versions were easy and reversions were common, about 4 in 10 (Table XIX). Fortunately after easy first versions and subsequent reversions, repeated versions were usually easy also. And repeated versions were not harmful to mothers or babies and did not increase the incidence of cords around necks. Very possibly, if versions wound cords around necks, reversions unwound them.

Therefore, the argument against external versions, on the ground that reversions occur too frequently, is not a serious one, as the versions may be repeated without danger until the presentations remain vertex.

The fear that premature labor may be caused by external version is groundless judging from this series, where the incidence of premature labors was actually less among the babies on whom versions had been performed than among all of the viable babies of the series on whom no versions had been performed, about 4 per cent in contrast to 6 per cent.

Finally, judging from this series again, external versions carefully performed do not endanger the lives of mothers or babies. There was no mortality among all the women and no loss from trauma of dystocia among all the babies, in and on whom these versions were performed or attempted, in a total of 368 versions performed and attempted unsuccessfully.

One woman only, in the series, showed symptoms causing anxiety. After version had been accomplished under anesthesia, slight bleeding appeared from the vagina. The mother's pulse and the fetal heart sounds remained unchanged. Very shortly after, labor started and ended safely for both patients. In this case too much force was used in performing the version, due to a badly taken anesthetic and consequent haste. Unwittingly, two of the most important rules governing

Of all conversions attempted, 92.5 per cent were entirely successful. Ten sections were performed because of persisting breech presentations. These were all on primiparas and comprised 3.5 per cent of the viable babies found in breech presentations.

Only six term babies of primiparas in single pregnancies were delivered vaginally as breech.

There was no loss from dystocia among any of the babies on whom external cephalic versions were performed and none sustained injury. And among all of the 258 viable babies found in breech presentations, the total mortality from dystocia was 0.4 per cent (excluding one consultation).

Conclusions

Fetal mortality in breech deliveries is unduly high. Every breech presentation, therefore, is a potential danger to the unborn child. This danger can be removed by early external cephalic version.

Reliance should not be placed upon spontaneous version. Individual babies will suffer when this fails.

Success in external versions depends upon early diagnosis of presentation by careful ante-partum palpation. When diagnosis is in doubt, it can usually be made by vaginal examination and always by x-ray.

External version should be performed gently and without haste. If it cannot be accomplished without force, the attempt should be abandoned. Carefully performed, the operation is not dangerous to fetus or mother. The fetus is in more danger from the breech presentation than from the version.

The operation is generally quite easy and usually may be performed without anesthetic if tried early. The most frequent cause of failure is delay in making the attempt until late in pregnancy. The next most frequent cause is extended legs of the fetus.

The best time for performing external cephalic version is in the sixth and seventh calendar months,* and breech presentations should not be allowed to persist beyond the seventh month without attempts at version. After this time, spontaneous versions are less likely to occur and artificial versions are more likely to require anesthesia and to be failures.

An obstetrician who lets a pregnant woman in his care go to term with a breech presentation undiagnosed, has usually not rendered the best service to his patient.

External cephalic versions, systematically employed, can reduce the fetal mortality following breech presentations to approximately that following vertex presentations.

*In a previous article,¹³ I stated that the best time for performing external cephalic version was in the seventh and eighth calendar months. Later experience has convinced me that the most favorable time is the sixth and seventh months.

In primiparas, while reversions are relatively rare, repeated versions are often difficult, especially if more than a week is allowed to elapse before second attempts. In multiparas, reversions occur frequently, but repeated versions are usually easy.

Method of Performing External Cephalic Versions

The maneuver of external cephalic version is usually not difficult, and it will be easier if the breech presentation is made out early. Careful and frequent abdominal palpation will generally reveal the presentation by the beginning of the sixth calendar month. If the presentation cannot be established by this method, vaginal examination in most instances will make it clear. If the presentation is obscure after both of these methods, an x-ray film will always show the presentation.

For the performance of this maneuver, the patient should be on her back relaxed physically and mentally. The bladder should be empty. All manipulation should be cautious and gentle. Haste or force should never be used. The tips of the fingers should be used rather than the whole hand. The fetal heart sounds should be listened to frequently and always before and after the attempt.

With a very small fetus, the head can often be turned quite easily, either clockwise or counterclockwise, until it reaches the transverse position, when it will descend suddenly and will be felt at the pelvic brim. The version is often surprisingly easy.

With a larger fetus, it is often best to work on the breech first. This is gently pushed up from the pelvic brim and then with the finger tips is directed slowly clockwise or counter clockwise. If it will not go readily in one direction it should be tried in the other direction. The fetus will turn more easily in flexion, that is, as if in a forward somersault. Except in very small fetuses, turning backward in extension is not possible. After the breech has been pushed upward to the transverse position, slight pressure on the head in the opposite direction will often bring success and the fetus will turn easily into the vertex presentation, when the head will be felt at the pelvic brim.

If version is not found possible on the first attempt, several days or a week should be allowed to pass before a second attempt is made. If several attempts fail, an x-ray picture showing the exact attitude of the fetus, may render version possible, either with or without anesthesia.

There should be few failures at external version in multiparas. In primiparas, there should be few failures if the attempts at version are made early in pregnancy. If the attempts are made late and in the presence of extended fetal legs, versions are difficult. The only chance of success then is by working on the breech, lifting it and directing it in the direction of the fetal back. With an x-ray film as a guide, success may be obtained by this method.

Needless to say, external versions cannot be performed in twin pregnancies. Other conditions, such as fibroid tumors, obesity, a small amount of liquor amnii and adhesions under abdominal scars, may make versions difficult or impossible, especially in primiparas.

Résumé of Results Obtained

In this series, three-fourths of the viable babies found in breech presentations were changed by external cephalic versions to vertex and were so delivered.

tion, and then the child is turned by lifting the breech away from the pelvic brim and flexing the head toward its thorax. If the reverse is tried, there will generally be failure.

Failure sometimes is due to the fact that the back is directly anterior or directly posterior. Lateroversion of the child is not possible. In such a case it is better to desist and see the patient again in a few days when conditions may be more favorable.

In my experience the commonest cause of failure is a frank breech with extended legs. In such the breech in the last two months of pregnancy may already be in the brim and cannot be lifted above it, and if it is freed the child cannot be swung around because its body is extended and splinted by the legs. When such a condition is suspected we have an x-ray taken. If this shows extended legs no further attempt at version is made. So I find that the great majority of my breech deliveries are frank breeches.

In all the years during which I have done external versions, I have encountered no case in which the child was compromised by the procedure, but it is important to auscultate the fetal heart during the procedure and stop if it becomes slow or irregular. We need fear no damage to the uterus or risk of separating the placenta if no force is used.

DR. GEORGE W. KOSMAK.—Dr. Ryder's paper deals with a procedure of definite importance as a prophylactic measure to avoid the assumed risks of delivery by the breech. The careful study of a large series of personal cases leads the author to the belief that for a successful vaginal delivery, the vertex presentation is essential. He performs or attempts an external version at any month when a breech is diagnosed and repeats it as often as necessary. However he admits that spontaneous version does occur. Would it not appear desirable to await this in the average patient? It occurred apparently in about 6 per cent of his cases. He claims success for the maneuver in 92.5 per cent of his cases, with no bad results, and that he failed in only 7.5 per cent. It would appear therefore that Dr. Ryder is a fairly successful and competent versionist. But Dr. I. S. Potter claims equally good results for his maneuver, which may be regarded as the exact opposite.

One cannot discuss the desirability of routine versions without endeavoring to analyze the reasons for breech presentations on the one hand and the results of breech deliveries on the other.

The incidence of breech presentations was stated by Pinard in 1889 to be 3.3 per cent in 100,000 labors, including premature and full-term babies. More recently the New York Lying-in Hospital claims an incidence of 4.72 per cent in about 17,000 deliveries. Naturally these estimates would be higher if a diagnosis was established before labor set in, and the spontaneous versions in the earlier months were included. The causes for breech presentations are stated by most writers on the subject to be manifold. The fetus, suspended in the liquor amnii should sink by its buttocks, so that if gravity were the only factor concerned, this ought to be the most frequent presentation which, evidently it is not, except with premature fetuses. Later on it must be assumed that there is some interference with the process of accommodation between the fetal ovoid and the uterus which would ordinarily bring about a head presentation. These natural forces are probably lacking in twin pregnancies and in hydramnios, because of increased uterine distention and flaccidity, which may also account for the greater frequency of breech presentations in multiparas. Their occurrence is also favored by any obstacle which opposes the engagement of the head, including pelvic deformities and hydrocephalus. There likewise seems to be a hereditary and a habitual tendency toward this condition in certain women.

In view of the foregoing why, in the absence of a definite abnormality in mother or fetus, may not a breech presentation be the most satisfactory adjustment in a

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Discussion

DR. BENJAMIN P. WATSON.—Too often nowadays papers are written and conclusions drawn from hospital records and case histories written by many different individuals, and rarely by the person who carries out the particular procedure recorded. That is why hospital and clinic statistics on this subject are of little value as compared with Dr. Ryder's.

In the paper just presented we have been given a precise account of one technique carried out and recorded by one man in a large series of cases over a period of many years. That establishes its great value.

With Dr. Ryder's general thesis I am entirely in accord, for I believe in and attempt external version as early in pregnancy as a diagnosis of breech presentation is made. We all grant that spontaneous version to a vertex often occurs in the sixth, seventh, or eighth month in primigravid and parous women, and even just before labor in a multipara. But if we can safely increase this number by a simple maneuver it is worth while trying it and repeating it again and again if necessary in any one case.

It may be argued that the necessity for doing cephalic version is not so great today as it was twenty years ago, because the infant mortality in breech delivery is not nearly so high today as it was then, thanks to our better understanding of the mechanism of breech delivery. In the Sloane Hospital over the last seven years, the uncorrected general fetal and infant mortality is just under 3 per cent, while the corrected fetal and infant mortality in breech deliveries is 5.3 per cent. Hence there is still a greater risk to the child in breech than in vertex delivery, and it is, therefore, worth while trying to correct it in the way advocated.

The risk to the child is not so great, however, as, in my opinion, to justify a cesarean section for breech presentation alone. Many women would have been saved the hazard of a section had a timely external version been done, for with a borderline pelvis a decision for or against section can be better made if the presentation is a vertex.

I, personally, never give an anesthetic when version is attempted for no force must be used. It is important to make an exact diagnosis of position before carrying out the maneuver. It is usually possible to locate the back by palpation and auscultation.

It hardly seems necessary to point out that the end results of a skilled obstetrician should be far better when compared to those of a teaching hospital or university clinic devoted to the training of young men. However, a brief consideration of a few statistics from the Lying-in Hospital for contrast may be interesting. In 25,678 consecutive deliveries at the Lying-in Hospital there were 1,176 viable prematures and term babies delivered as breech, an incidence of 4.5 per cent. The gross uncorrected fetal mortality among these breech presentations for the clinic as a whole, was 12.1 per cent, and divided was 7.1 per cent on the private service and 14.2 on the clinic service. If these figures are corrected on the same basis that the speaker has allowed for his own statistics, we then find that the gross combined corrected mortality is 3.5 per cent and once again divided, becomes 1.1 per cent on the private service and 4 per cent on the clinic service.

I am aware that a fair comparison between our figures and Dr. Ryder's cannot be made inasmuch as the number of breech presentations delivered at term on our clinic service is about thirty times greater than his and the end results on our private service, although comparable in number, represent the experience of many obstetricians rather than an individual's. Nevertheless, Dr. Ryder's arguments for cephalic version as they have been presented in the light of his own experience are impressive and cannot be refuted until a comparable series is produced by one who will show that the end results are as good or better without attempting to convert breech presentations to vertex by external or cephalic version.

DR. HERVEY C. WILLIAMSON.—In 1,500 consecutive deliveries in my own practice, there were 60 breech presentations, an incidence of 4 per cent. Four cesarean sections were performed, two electively for funnel pelvis and two were of the Latzko type. In both of the latter patients the labor was complicated by premature rupture of the membranes, a Voorhees' bag was inserted but effective labor did not occur. Perhaps these two labors were not well managed; however, the ultimate outcome was satisfactory. Dr. Ryder performed 10 cesarean sections in 45 breech presentations.

There were 51 living babies delivered vaginally, four died after birth and one was a stillbirth. Two of these babies were premature twenty-four to twenty-six weeks' gestation. One mother had Hodgkin's disease, the other a low implantation of the placenta in the uterus. Another baby died on the fourth day of life following an operation for intestinal atresia. The fourth baby, weighing 4 pounds 13½ ounces, died on the second day following delivery. At autopsy a tentorial tear and cerebral hemorrhage were found. The stillbirth was the result of an intrauterine death of a large fetus in an elderly primipara.

A Voorhees' bag was used in nine patients where the membranes had ruptured before labor. The results in seven were satisfactory, two resulted in the Latzko operations mentioned. Forceps applied to the aftercoming head were generally used and a mediolateral episiotomy was usually performed.

DR. E. EVERETT BUNZEL.—We are able to avoid many breech deliveries by doing external cephalic version. One should not, however, do the version at the fifth or sixth month, but rather in the seventh or eighth month of pregnancy.

You may, of course, wrap the cord around the neck of the baby by doing a version, but you may also unwrap it if such a condition existed previously.

I disagree with the view that most breech presentations will turn spontaneously if they are left alone because I have had a few cases in which even in the eighth month of pregnancy, it was impossible in the office to convert a breech to a vertex. In such instances I have taken the patient into the hospital, have given her chloroform, and have then successfully converted the breech into a vertex, and finally had a vertex delivery unassisted.

Breech delivery of itself carries a definite fetal mortality, whether the patient is a multipara or a primipara. At the Sloane Hospital we have found a greater

particular case? And why should we attempt to disturb nature's mechanism or how can we tell that our manipulative procedures will improve matters? In a general sense the prognosis in breech presentation is considered worse for the child especially in primiparas, the gross fetal mortality being stated by various authors to be from 10 to 35 per cent, including prematures, full-term and neonatal deaths. Goethals in his series from the Boston Lying-in Hospital (1,242 cases) found a mortality of 6.9 per cent in full-term uncomplicated pregnancies. Stander at the New York Lying-in Hospital reports an uncorrected fetal mortality rate of 13 per cent for all breech deliveries. Charles A. Gordon in a comprehensive study of 3,000 breech deliveries found a gross mortality of over 20 per cent but admits that the presentation itself seemed responsible for only about one-third of these deaths. Stander in his last edition of *Williams' Textbook* states that as the result of collected experiences, the risk to the child even in uncomplicated full-term breech deliveries is more than twice that associated with vertex presentations.

It is unnecessary to discuss further the reasons for this higher mortality rate. If it can be avoided by preventive measures, these must be given due consideration. However, in my belief, the mere diagnosis of a breech, especially in the earlier months, should not necessarily call for the substitution of a procedure, which in itself is not invariably successful or may produce complications of equal risk. Spontaneous delivery of a breech is readily possible; Gordon and others have demonstrated that interference with normal mechanism and rapid extraction frequently is the *real* cause for a fatal outcome in many cases. Adequate knowledge of the mechanism and the proper handling of the case would appear all important. In primiparas with unsatisfactory cervix dilatation the Voorhees' bag has proved very satisfactory in my experience, combined if necessary with a median episiotomy at the proper time.

Dr. Ryder is to be congratulated on his good results. The question remains whether a general direction broadcast to all practitioners of obstetrics would prove equally safe. There is always a risk of cord involvement, of possible placental separation and Dr. Ryder's recommendation that external version be done at any month of pregnancy and repeated at varying intervals must be compared with the plan of others who would limit it to full term and before the membranes are ruptured. The question will never be fully decided as long as the adherents of either a conservative or a radical policy toward a breech presentation, believe that in their hands, either method is satisfactory. It would be difficult to convince Dr. Potter and his followers, for example, that all babies should not be born by the breech unless delivery takes place before they can do a prophylactic podalic version to which, notwithstanding the claimed results, most of us will not subscribe. It will be equally difficult to persuade those who are convinced that a vertex presentation is essential for a successful delivery, to modify their views.

DR. ANDREW A. MARCHETTI.—The value of converting breech to vertex presentation by external or cephalic version has been accepted and disputed by many. A survey of the more recent literature indicates that the advocates of the procedure far outnumber its opponents. Among those who do not advocate it may be mentioned Dunbar, Meyer, Sherman, and Hanley and Rosenblum. Sherman believes that proper conservatism in the treatment of breech presentation would do more to lessen the fetal mortality than routine external version or the use of cesarean section. Hanley and Rosenblum feel that the procedure is too dangerous as long as the location of the placenta is uncertain. However, it appears that these particular objections in addition to other general ones which Dr. Ryder has alluded to, are outweighed by the fact that even in the hands of the best, from all the available statistics, the fetal risk associated with the vaginal delivery of breech presentation is considerably increased as compared to delivery of the vertex.

DR. WILLIAM E. STUDDIFORD.—I favor external version, but I think it carries some danger with it. I have seen several patients who ruptured their membranes within twenty-four hours of the time the external version was carried out. The possibility of this accident is a very excellent reason for not performing this procedure until the fetus is at least in the thirty-sixth week of gestation. In addition, a more serious accident was seen several years ago in a case in which external version was attempted in the clinic of Bellevue Hospital. No violence was used, but the procedure failed. Within twelve hours the patient was in the hospital with a complete separation of the placenta.

The explanation for the very successful results which Dr. Ryder has been able to obtain may be found in the fact that he attempts external version very early in a great number of breech presentations which otherwise would turn over spontaneously if left alone. I believe if he postponed the procedure until the thirty-sixth week of pregnancy the number of successful results would drop sharply and also the number of opportunities to carry out the procedure. Although I have been trying to carry out this maneuver at the thirty-sixth week for a good many years, I doubt if I am successful in more than 50 or 60 per cent of instances.

While many failures can be accounted for by difficulties in manipulation of the fetus due to thickness or resistance of the maternal abdominal wall or to excessive amniotic fluid, others appear to be due to the attitude of the fetus. Dr. Ryder has already pointed out the role of extended fetal legs in preventing successful external version. X-ray study of the persistent breech presentation frequently shows other peculiarities of attitude such as extension of the arms, extension of the head and occasionally extension of the whole body.

DR. RYDER (Closing).—In my opinion, early external cephalic versions will save the lives of many babies who otherwise would be lost in breech deliveries. This is an established fact.

Spontaneous version occurs in the majority of cases. But when it does not occur, the choice must be made between breech delivery, with an approximately 10 per cent chance of fetal loss, and section with an increased risk to the mother.

I was pleased to hear Dr. Watson say that he attempts external version as soon as he makes the diagnosis of breech presentation. If he believes in early external cephalic version, he undoubtedly teaches it. He will thus be the means of saving the lives of many babies, through his students, in the years to come.

If artificial version is accepted as a sound prophylactic measure in breech presentations, the question arises as to the time when it should be attempted and the conditions under which the attempt should be made. Dr. Cosgrove and Dr. Studdiford argue that early artificial versions are unnecessary as most breech presentations will change spontaneously to vertex later. In my series, there were no failures at conversion to vertex before the eighth month. After this time one-fifth of the attempts were failures. Judging from my experience, therefore, it would seem reasonable to attempt versions before the eighth month. And I was glad to hear Dr. Marchetti say that he advocates the seventh month.

Dr. Watson says that he never attempts external versions in frank breech presentations and that he never uses anesthesia for an attempt. Undoubtedly, external version is much more difficult in frank breech presentations. In primiparas, 75 per cent of my failures at conversion were in frank breech presentations. But there were no failures in frank breech presentations in multiparas, and none in primiparas before the eighth month. Thus, frank breech presentations would seem to make external versions especially difficult or impossible only after the eighth month in primiparas.

mortality in multiparous than in primiparous breeches. I cannot understand this, but the statistics will back me up in that statement.

DR. SAMUEL A. COSGROVE.—The statement that more can be done toward reducing the danger of breech delivery by proper management of the breech is irrelevant in tonight's discussion. It can be assumed that Dr. Ryder and Dr. Watson, for example, know how to deliver breeches properly. The question, therefore, is: In such a man's hands can babies be saved by adopting a prophylactic measure to prevent having to handle them in a presentation which is universally shown by statistics to be more dangerous than cephalic presentation.

The experience of most of us demonstrates that external cephalic version prior to the onset of labor is a relatively safe procedure. Yet it is not, I believe, quite so innocuous as Dr. Ryder would have us suppose. I have seen abruption of a low implantation of the placenta result from my own attempts to do such a version. In nearly all such manipulations, if you watch the fetal heart carefully, you will note that the baby does not like what you are doing. Dr. Watson also pointed out how carefully you must watch the fetal heart and desist in the operation if the fetal heart so indicates. If the risk to the baby is definitely less than the risk of permitting the baby to go to term, then it is certainly a procedure that should be thoughtfully and routinely employed.

The only question that comes up in this practice as Dr. Ryder has described it, is the time of its employment. It has not been my custom to attempt this procedure as early as the breech presentation can be diagnosed. It seems to me that a little later in pregnancy, perhaps toward the end of the eighth month, is the more nearly optimum time. It is true that the percentage of success at that time will not be as high as it will be if it is employed earlier. You will, however, have had the advantage of nearly all of the spontaneous versions without the necessity for artificial interference and you will be able to accomplish the operation in a majority of the cases.

I would like to ask Dr. Ryder whether his 92 per cent of successes means success in 92 per cent of the babies on whom he has attempted the operation, or 92 per cent of the operations. In some cases the operation appears to have been applied several times to the same baby.

DR. RYDER.—It refers to the same babies. In some instances I turned the baby three or four times.

DR. D. ANTHONY D'ESOPPO.—It is rather interesting to note the incidence of breech deliveries at the Sloane Hospital and compare it with Dr. Marchetti's figure at the New York Hospital. This is especially valuable because recently we had an opportunity to study the fetal mortality in both institutions and found that our statistical procedures were comparable in every way.

At the New York Hospital, where they apparently do not perform external version, the incidence of breech delivery is 4.5 per cent, and at the Sloane Hospital in the last 10,000 deliveries the incidence is 3.8 per cent. It appears therefore that irrespective of whether you do external version or not you end up with about the same number of breech presentations. These figures seem to point to the fact that the breech which can be successfully turned will, in most instances, undergo spontaneous version if left alone.

DR. E. EVERETT BUNZEL.—Some of the cases which are admitted to our service in labor with a diagnosis of vertex presentation previously made in the prenatal clinic are found to be breech presentations. I think this is because the interns sometimes fail to diagnose a breech presentation in the ante-partum clinic. As a result of this, an external version is not done and therefore we have a certain number of unnecessary breech presentations to deliver.

the cervix. Twenty-five per cent had retroversion of the uterus. Twenty-six patients (28 per cent) had bilateral adnexal masses, 42 patients (44 per cent) had bilateral involvement of the adnexa with a unilateral mass and 26 patients (28 per cent) presented a unilateral mass with no palpable thickening or exudate on the other side. The cervical smear was positive for gonococci in 19 patients, doubtful in 15 more, and negative in 60 patients.

Determination of red cell sedimentation rate was performed, using the Cutler tube. Of our 54 hospital patients, all but two had increased sedimentation rates, and of the 40 clinic patients, 32 had increased rates (Table V). Thirty of the 40 clinic patients had temperatures above normal (Table V).

These 94 patients received a total of 1,666 treatments. Table VI indicates the number of treatments given both in the hospital and in the

TABLE VI

TOTAL	NUMBER OF TREATMENTS			HOSPITALIZATION		SIZE OF MASS ON DISCHARGE		
		In Hospital Patients	In Clinic Patients	Days	Patients	No Change	Smaller	Resolved
Hospital (54)	0	2	3	1-10	11	1	47	6
	1-5	21	5	11-20	23			
	6-10	21	23	21-30	15			
	11-15	9	12	31-40	5			
	16-20	1	6					
	21-30		5					
Clinic (40)	1-5 (0 pts.) 6-10 (6 pts.) 11-15 (23 pts.) 16-20 (10 pts.) 21-25 (1 pt.)							

TABLE VII

TOTAL	FOLLOW-UP IN CLINIC			REINFECTION IN CLINIC
94	3-12 mo.	12-24 mo.	24+ mo.	
Hospital (54)	38	15	1	4
Clinic (40)	29	11	0	5

TABLE VIII

TOTAL	ASYMPTOMATIC					WHEN SED. RATE BECAME NORMAL (0-18 MM./60 MIN.)				
	On discharge	1-6 wk.	6-18 wk.	18-30 wk.	Failure	On discharge	1-2 wk.	3-4 wk.	5-7 wk.	No change
Hospital (54)										
	8	23	16	5	2	9	24	15	5	1
Clinic (40)						On admission	1-2 wk.	3-4 wk.	5-7 wk.	No change
		23	14	0	3	8	15	14	3	0

Anesthesia is seldom necessary for the performance of external versions, but occasionally success can be attained under anesthesia where failure had resulted without it. In my series, only 4.4 per cent of the conversions were accomplished under anesthesia, but all of these successful conversions with anesthesia had previously been failures without it.

Some obstetricians still do not believe in prophylactic external cephalic versions and prefer to chance later breech deliveries when necessary, claiming that their results are satisfactory. In a small series of breech deliveries, this may be so. But statistics from all over the world show that in any large series, the fetal mortality is too high, even in the best of hands. Dr. Irving Potter of Buffalo who conducts more breech deliveries than any other man and who has thus acquired remarkable skill, told me in 1923 that his fetal mortality in breech deliveries following primary breech presentations was 9 per cent in primiparas.

In my series, 258 babies found in breech presentation were delivered with a fetal mortality from dystocia of only 0.4 per cent (omitting 1 consultation). Any one by the systematic use of prophylactic external versions should obtain equally good results. But without prophylactic versions, I doubt if it is possible unless an unduly high proportion of sections are performed.

CARCINOMA AND SARCOMA IN THE SAME UTERUS

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THE case about to be reported is of interest from at least two points of view. First, there is the very late appearance of the first suggestive symptom of carcinoma of the corpus uteri, due to cervical occlusion, and second, the peculiar nature of the primary lesion and of the secondary metastases. Whether the case should be called one of carcinoma and sarcoma in the same uterus, or whether it should be classed as a carcinoma with a bizarre type of anaplasia is a question open to discussion.

The patient when first seen by me was sixty-three years of age. She had had four children. At the end of her reproductive period, the cervix had been repaired and the uterus suspended. The menopause occurred at the age of forty-eight and thereafter she had had no vaginal discharge of any kind until the day before I saw her, which was April 1, 1940. On March 24 she had had an attack of severe abdominal pain accompanied by nausea. This pain recurred the following day and the abdomen became considerably distended. There was marked tenderness over the pelvic brim on the left side. The temperature was 100.4° F., and there was a leucocytosis up to 13,500. A diagnosis of acute diverticulitis was made and the patient kept at rest. In the succeeding four days the pain became less with occasional exacerbations. On March 31 the patient was allowed out of bed. She had a sharp recurrence of pain and passed a large quantity of tomato juice-like fluid from the vagina. With the escape of this fluid the pain subsided and she felt perfectly comfortable though greatly alarmed.

*Presented at a meeting of the New York Obstetrical Society, November 10, 1942.

I saw her for the first time on the following day, and on examination found as follows: "The vagina is narrow and contracted; the cervix is rather large, no external os can be felt at the apex, but toward the left side is a small opening which might be the os or an artificial opening through which the discharge is still exuding. The uterus is definitely larger than it should be at her age, and to the right of it there is a tense swelling, five to six centimeters in diameter. The left fornix feels indurated." Cultures of the discharge showed it to contain a hemolytic streptococcus so all further exploration was deferred until the organism was typed. As it proved not to be Group A, surgical exploration was carried out on April 4, the possibilities before us being that the case was one of cervical occlusion with pyohematometra, cervical occlusion with adenocarcinoma of the corpus, or possibly a carcinoma of tube or ovary with a break through into the side of the uterus and cervix.

The external os at the apex of the cervix was completely occluded. A probe introduced through the ragged opening on the side of the cervix passed into the uterine corpus. No further exploration from below was done as it did not seem wise to do a diagnostic curettage or to apply radium should a curettage reveal carcinoma. Accordingly the abdomen was opened. There were dense adhesions of the omentum to the uterus, which was as large as a two months' pregnancy, and to both adnexa; the right ovary was replaced by a cyst the size of a lime. What was taken to be the left ovary was a thick mass adherent to the back of the broad ligament which latter was indurated. The tubes were free. The round ligaments were thick and attached to the anterior abdominal wall. After freeing the several organs, a complete hysterectomy was done with wide removal of both adnexal masses and a good cuff of vagina. The patient had an uneventful convalescence from the operation.

Pathologic Report.—The uterus, measuring 7 by 9 by 4 cm., contained a few small subserous fibromyomas. The endometrial cavity measured 5 by 9 cm. The lining was shaggy and hemorrhagic. On the posterior wall there was an area 6 cm. by 3.5 cm. which was raised above the surface, was covered with fungating seminecrotic material and was firmer in consistence than the surrounding endometrium. Below the internal os the cervical canal was 5 cm. in length and was widely dilated, measuring at its middle 2 cm. in diameter. Almost 1 cm. below the internal os was a thinned-out area in the left cervical wall which led downward to an irregular perforation 3 mm. in diameter, which opened on the vaginal aspect. The external os was so narrow and stenosed that the finest probe could be pushed through it from above only with considerable pressure.

Right tube was 6 cm. long by 0.7 cm. in diameter. Fimbria were present and lumen patent. Serosa was smooth and glistening. Moderate amount subserosal injection was seen.

Right ovary had been converted into a large dark red hemorrhagic cystic mass; inner wall was stained deep red from old hemorrhage, and cyst measured 4 cm. in diameter. Entire ovary measured 6.5 by 4.5 by 3.5 cm. On section, ovarian tissue appeared edematous and somewhat gelatinous; there were cystic areas which exuded, on incision, a dirty yellow mucoid substance. No normal ovarian tissue was seen.

Left tube was 8 cm. long by 0.6 cm. in diameter; fimbria were present. Serosa was somewhat shaggy due to few adhesions; in places it was

smooth and glistening. Moderate subserosal injection was noted and a small area of subserosal hemorrhage. Accompanying the tube was an irregular pink hemorrhagic, rather firm mass, 5.5 by 3.5 by 2 cm. Surface appeared furrowed and scarred; on section it was yellowish gray in color. There was a small hemorrhagic cyst at one pole 1 cm. in diameter. Another area of the mass was quite edematous.

Fig. 1 shows, under low power, the tissue of the above mentioned raised area on the inner surface of the posterior wall of the uterus. It has all the characters of a typical adenocarcinoma of the endometrium. Figs. 2 and 3 are low and high power views of an area in the posterior uterine wall beneath but completely separated from the surface tumor.



Fig. 1.—Section from posterior wall of uterine wall. $\times 80$.

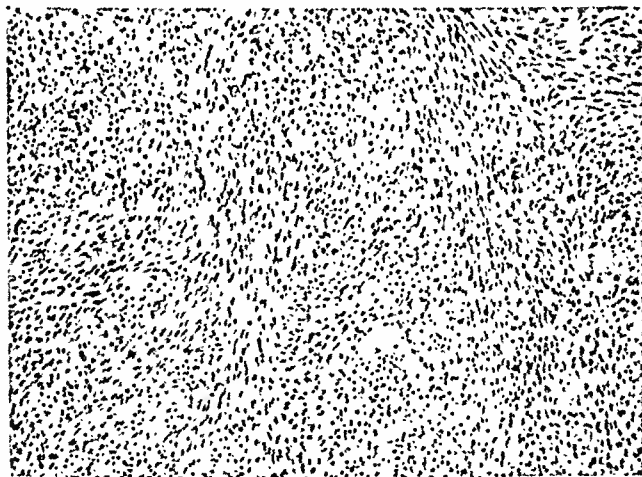


Fig. 2.—Section from posterior wall of uterus deep to the surface lesion (low power). $\times 80$.

These sections would, if taken by themselves, be classed as sarcoma. Fig. 4 is a section of the ovarian mass on the right side. It shows adenocarcinoma of the same type as the original tumor in the endometrium. Fig. 5 is a section from the left adnexal mass. The appearances here are strongly suggestive of sarcoma.

Such was the picture of the original tissue removed at the time of operation. The operation was followed by a course of deep x-ray ther-

apy administered through four portals to a total of 1,800 r. This course was completed on August 4. Examination at that time showed the abdominal and vaginal wounds completely and firmly healed. At the vaginal roof toward the left side a rounded nodule, the size of a pea, was felt. It gave the impression of being cystic, and it was thought it might be a small hematoma or inclusion cyst. However, a month later

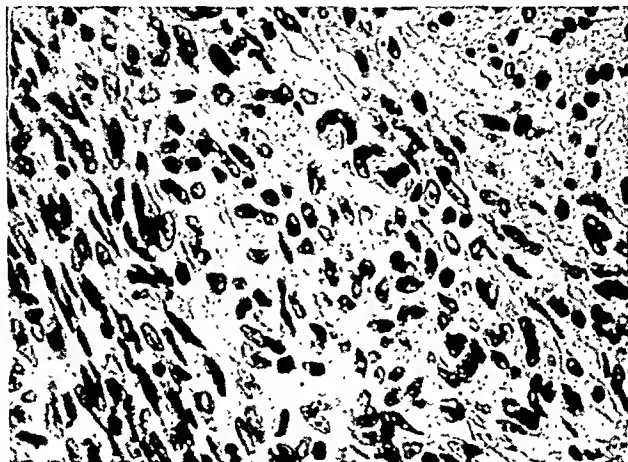


Fig. 3.—High power view of Fig. 2. $\times 150$.



Fig. 4.—Section from right ovarian tumor. $\times 80$.

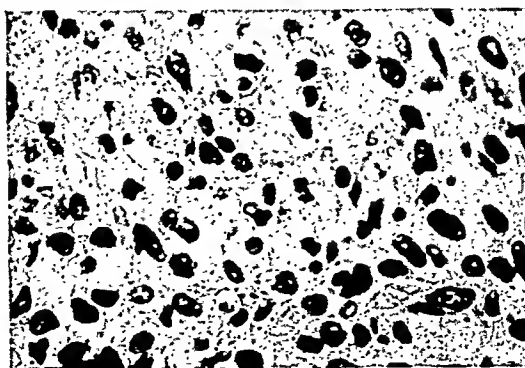


Fig. 5.—High power of tumor in left ovarian mass. $\times 150$.

examination revealed a soft, polypoid mass the size of a cherry, projecting from this area and attached by a narrow pedicle. It has the clinical appearances of a sarcoma rather than a carcinoma. A small biopsy was taken which proved it to be malignant, so on September 10 the whole mass was removed by cautery, and radium applied at the site of removal. The dose administered was 1,500 mg. hr. This resulted in almost complete agglutination of the walls at the roof of the vagina, and there was no more vaginal discharge.

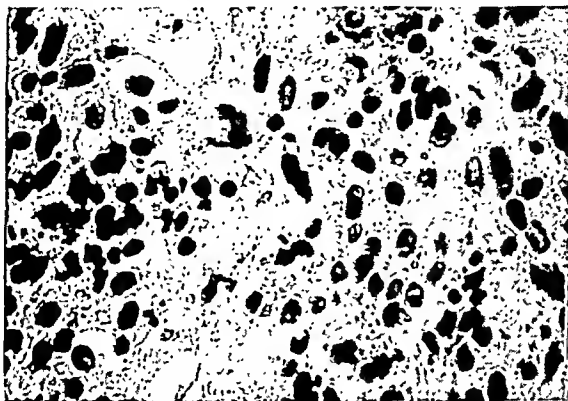


Fig. 6.—Vaginal recurrence, high power. $\times 150$.

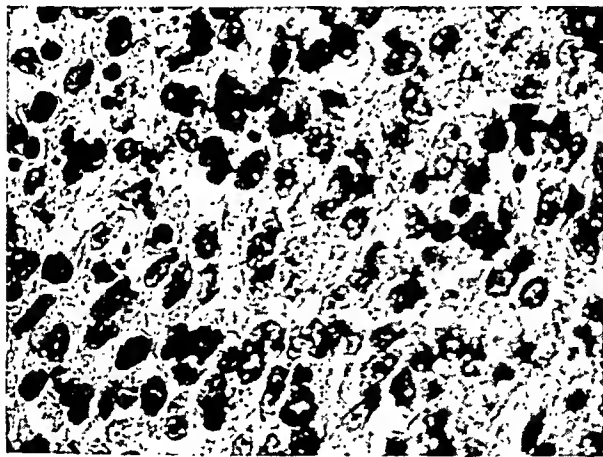


Fig. 7.—Bladder tumor. $\times 100$.

Sections from this vaginal metastasis or invasion are shown in Fig. 6. They have the characters of a sarcoma rather than a carcinoma.

Between October and January she had recurring attacks of backache and some urinary frequency. X-rays of the bones showed no evidence of metastasis. She put on considerable weight. On January 10 she had severe bladder discomfort and noticed blood in the urine. Vaginal examination was now impossible, owing to the agglutination of the wall, but rectoabdominal examination revealed distinct thickening in the region of the vaginal roof. The hematuria continued. On January 20 Dr. George Cahill did a cystoscopy and found "a round mass arising from the floor of the bladder in the posterior and midtrigonal region, more on the left side. The rounded surface is irregular and here and

there the surface is broken with blood attached." The appearances were not those of an ordinary carcinoma of the bladder. A small biopsy was taken. An intravenous pyelogram showed no obstruction to the ureters at this time but the position of the tumor was such that obstruction was certain to occur sooner or later. The patient ultimately died in August, 1941, sixteen months from the time of the original operation.

A section from the biopsy material from the bladder tumor is shown in Fig. 7.

Dr. M. M. Melicow, of the Department of Urology, in his report states: "The malignancy does not resemble the usual bladder tumor. It is impossible to state from the slide whether it is a sarcoma or a carcinoma."

This case has aroused a great deal of interest in our Department and it is presented for consideration and discussion. Dr. A. Purdy Stout, of the Department of Surgical Pathology, has gone over all the sections very thoroughly. His opinion carries great weight so I quote him:

"The uterus is the site of a relatively well differentiated adenocarcinoma of the endometrium. It does not appear to penetrate deeply and in general it tends to form glandular structures lined by cylindrical cells. There are also two leiomyomas and the cervix is the site of a moderate degree of chronic endocervicitis. In one section of the uterine wall beneath the carcinoma there is a focus deep in the musculature, composed of relatively undifferentiated cells which have insinuated themselves between some of the muscle fibers. This does not appear at all like the primary growth, but it probably represents a metastasis or an extension from it.

"Sections from the right adnexa show that the right ovary is filled with carcinoma resembling that in the uterus. The broad ligament is invaded by tumor but the right tube is negative.

"Sections from the left adnexa show that there is tumor in both the left tube and ovary and that the broad ligament is very extensively invaded with many areas of necrosis. The tumor in this situation has changed its morphological appearance to a remarkable degree. In the tube and ovary, instead of it being a simple adenocarcinoma, the growth now consists of atypical glands and a sarcoma-like stroma which forms interlaced strands of very anaplastic spindle-shaped cells with vast numbers of mitoses. In the broad ligament this apparent carcinosarcomatous effect is reproduced, and in one zone an entirely different type of undifferentiated carcinoma appears, made up of small, rounded, deeply hyperchromatic cells showing mitoses in almost incredible numbers, averaging ten to fifteen per high power field.

"I believe that this should be considered as altogether a carcinoma of the uterus with an extraordinarily marked degree of anaplasia. Whether the apparent sarcomatous areas represent anaplastic carcinoma cells or a bizarre, non-tumorous proliferation of stroma cells, I am unable to state.

"I believe that this must be regarded as an extremely malignant type of growth and that the prognosis is very grave."

Discussion

DR. ANDREW A. MARCHETTI.—The sections which were shown were not altogether convincing to me as representing real adenocarcinoma of the endometrium. The sarcomatous changes impressed me much more, and, judging from the history

of the patient as well, it appears to me that this may have been an endometrial sarcoma of the uterus with metastasis. You may see, of course, in these sarcomatous areas of endometrial stroma a sort of hyperplasia of the glands without that being an adenocarcinoma.

What else impressed me was the metastasis. Usually in a mixed tumor, such as the present one, we find that the carcinoma is the one which metastasizes to the far distant organs. For this reason I suggest that this is primarily an endometrial sarcoma of the uterus with metastasis to the ovary and, ultimately, to the vagina.

DR. BENJAMIN P. WATSON.—There is no question about the adenocarcinoma in the uterus and there is no question about the adenocarcinoma in the right ovary. I believe Dr. Marchetti will grant that these were adenocarcinoma. I differ also from Dr. Stout's opinion that the original lesions were adenocarcinoma and that the extension and the metastases have simply taken on this extremely bizarre appearance suggesting sarcoma, for, *clinically*, the recurrence in the vagina was not carcinoma, it was sarcoma. It was a soft, polypoid growth which is typical of sarcoma, not the firm, ulcerated lesion of carcinoma. Dr. George Cahill, urologist, in doing the cystoscopy, and noting the bulging tumor in the bladder with the rounded contour, said, "This is not carcinoma, it is sarcoma."

RECONSTRUCTION OF THE OVIDUCTS IN THE HUMAN*

Results Obtained With the Use of a New Technique

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IN AUGUST, 1939, a report was made in this JOURNAL¹ on the experimental reconstruction of occluded oviducts in the *Macacus rhesus* monkey. The technique described then was one devised by the author and was based upon the use of a new surgical agent, bovine allantoic membrane. The results obtained and reported were sufficiently encouraging to warrant the use of the described technique in the human being. The purpose of this paper is to report the results obtained in a short series of such reconstructive operations.

Technique

This has been changed little since the original report on the experimental work. All cases reported are those of reconstruction of the fimbriated end of the tube. Due to a lack of suitable cases, the technique originally advocated for reconstruction of tubes with midpoint obstructions has not been carried out.

Only two special instruments are necessary in order to carry out the procedure to be described. One is a large caliber three-inch spinal needle with trocar, the end of which has been ground to a round, dull point. Second, a long, fine, flexible straight needle five inches in length, which any jeweler can make from piano wire or other high quality steel.

The technique consists of six basic steps: (1) The tube is freed of adhesions along its entire length so that no external adhesions produce kinks or constriction of the tube. (2) The fimbriated end of the tube is carefully examined in an effort to find a small white point, which usually

*Read at a meeting of the New York Obstetrical Society, December 9, 1942.

denotes the point of closure of the ostium. It has been found advantageous to start blunt dissection at this point, in an effort to open up the obstructed ostium of the tube. If it is possible to re-establish patency by blunt dissection, it will be found, in a great many cases, that the fimbriae may be massaged out, so that it is not necessary to sacrifice any of these important tubal structures by amputation. The most convenient instrument to use for this blunt dissection is a straight or curved fine-pointed "mosquito" forceps. Any local masses or scar tissue which decrease the circumference of the tube at this point are dissected free. If it is possible to avoid suturing and tying bleeders, tissue destruction will be held to a minimum. (3) With the fimbriated end of the tube thus opened, retrograde insufflation is carried out. This is done by injecting air into the fimbriated end of the tube by the use of a ball-tipped asepto type syringe. If difficulty is experienced in this procedure,

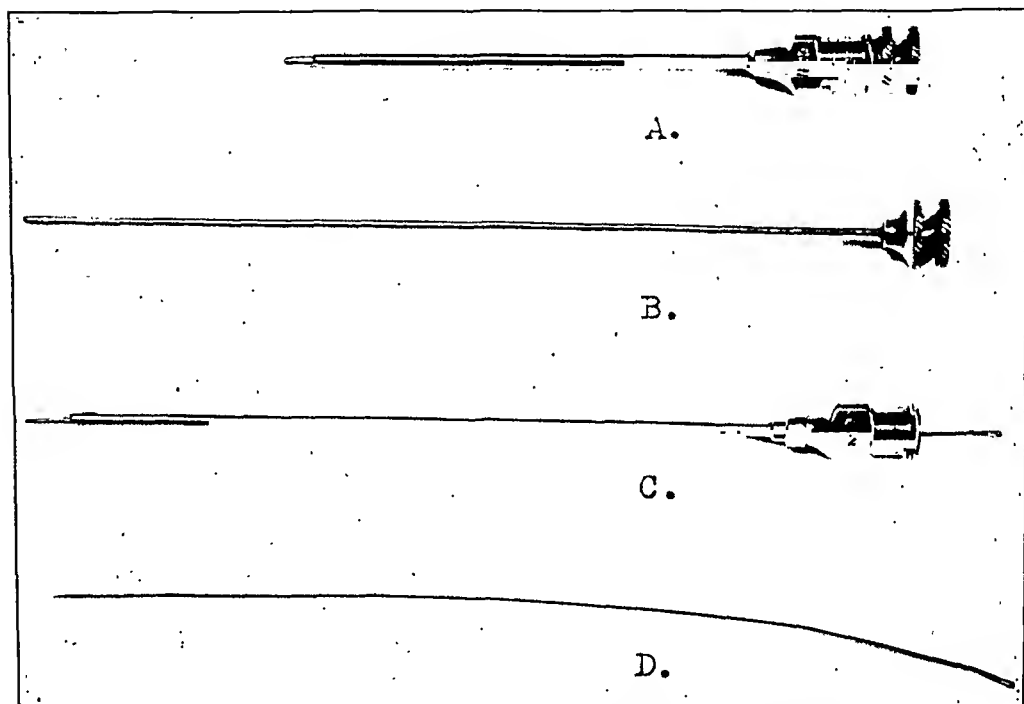


Fig. 1.—Type of trocars and needles used in the operation.

or if it is felt in any individual case that it entails too much trauma of the tubal tissue, then insufflation may be done by introducing the point of an ordinary intramuscular-type needle through the wall of the uterus into the uterine cavity. Pressure is applied to the cervix from above while the operator injects air into the uterine cavity, watching it progress along the length of the tube. Now that tubal patency has been established, the fourth step is in order. The cannula is cautiously manipulated down the lumen of the tube for a distance of 3 or 4 cm. The inner trocar is removed, while the cannula is held in this position. The long, flexible straight needle with attached 0000 chromic catgut is passed through this cannula until the end of the needle perforates the tubal wall. Its end is grasped and held tightly while the cannula is withdrawn from the tube. The needle is gently pulled through the point of perforation. A long piece of catgut now enters the fimbriated end

of the tube and lays in the lumen until it perforates the tubal wall some 3 or 4 cm. toward the uterus. (5) A sheet of allantoic membrane four by six inches is gathered in the center in the same way one would pick up the center of a handkerchief, and the distal end of the suture is tied about this central point. The fimbriated end of the tube is held between the finger tips while traction is exerted upon the proximal end of the suture, resulting in the passage of a considerable portion of the allantoic membrane into the lumen of the tube. The suture is then fastened to the adjacent mesosalpinx, in order to prevent extrusion of the membrane due to tubal peristalsis. (6) The allantoic membrane which protrudes from

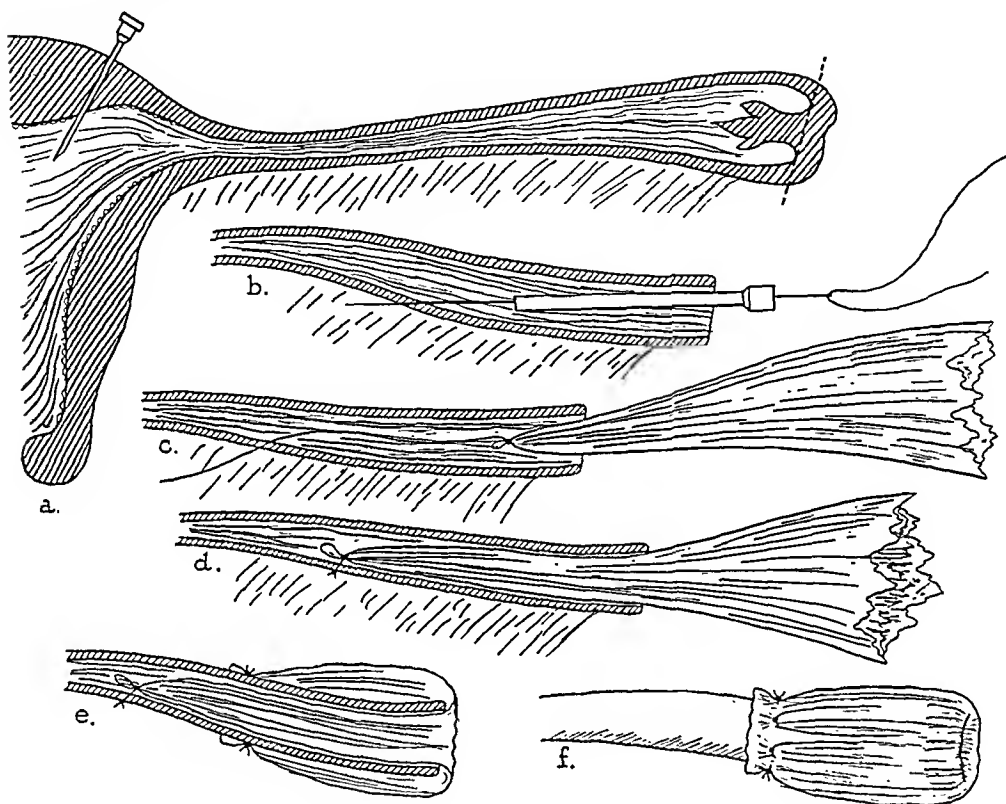


Fig. 2.—Schematic outline of technique employed.

the ostium is then spread outward and downward over the serosa of the tube in much the same manner as one would close an umbrella upon the handle. The membrane will completely cover the raw orifice of the tube and, at the same time, protect the distal portion of the tube against the formation of adhesions to surrounding structures. The various corners of the free edge of this membrane are then attached to the serosa and the mesosalpinx with fine interrupted catgut sutures. This completes the operation. While minor variations are occasionally necessary, the six steps described amply cover the basic technique.

Results

Twenty-eight cases on which this procedure has been carried out will be considered. This is the total number of operations done up to six months ago. Twenty-four of these cases have been followed for a minimum of six months; 4 have entirely disappeared from observation with results unknown. Of the 24, 21 were patent three months after

TABLE I. RESULTS OBTAINED

Operations	28
Followed 6 or more months	24
Number patent	18, or 75%
Possible pregnancies	17
Patients pregnant	2, or 8.7%
Number of pregnancies	3, or 13%

operation, but 3 were subsequently found to have occluded tubes. Location of occlusion in one is unknown. In the other two the point of occlusion recurred in the fimbriated end as confirmed by lipiodol in one and subsequent operation in the other. This last patient was reoperated and the same plastic procedure again carried out. Insufflation shows patency at 130 mm. pressure. It is interesting that the fimbria were found inverted for the second time in this patient, so that the technique was definitely faulty in this case. Of 24 patients followed for six months or more, then, 18 have patent tubes. In no case has it been necessary to use pressure in excess of 135 mm. of mercury to establish this post-operative patency. The average pressure required was 90 mm. of mercury. Of these 18 patients, 17 have had ample opportunity to become pregnant and no defect has been established which would be sufficient to prevent this outcome. Husbands have been carefully checked in each case previous to operative intervention. In spite of these precautions, only two patients have become pregnant, for a total of three pregnancies, one resulting in a normal term infant; the other aborted at less than three months and is now again in her third month of pregnancy, as confirmed by clinical examination and Asehheim-Zondek test. There have been no ectopic pregnancies. Occasional delayed menses have been common to many of the patients, but must be ascribed to the tremendously important psychological effect of anticipation of pregnancy rather than to conception and abortion.

Conclusions

Three pregnancies in two patients have occurred as the result of 23 operations, roughly, 8.7 per cent. This compares favorably with 6.6 per cent found by Greenhill² in a national survey of results of tubal plastic operations. This low percentage of results, however, detracts from the rather impressive record of patencies obtained. The reason for such a low percentage of successes has not been determined but probably lies in the number of hydrosalpinx cases operated upon. It seems logical to assume that the amount of disturbance of the tubal muscularis, plus the typical flattening of the mucosal cells, with disappearance of the cilia are all processes which cannot be reversed by surgery. It is noteworthy that the only patients to become pregnant exhibited more resistance to the passage of air through the tube than did many others who have not become pregnant. The low pressure required to pass gas through these tubes may well be an indication of the paralysis and damage which has taken place previous to operation. It is a source of regret to the reader that advantage has not been taken of the kymographie readings which could have been obtained before and after reconstruction. It may well

clinic. It will be noted that 44 patients (81 per cent) were able to leave the hospital after 10 treatments or less. No patient was discharged until her temperature had been normal for six days and she had been ambulatory for two days with no subsequent rise in temperature. Neither the sedimentation rate nor the size or extent of the pelvic mass governed the date of discharge. In fact, only 9 hospital patients had normal sedimentation rates on discharge and in only 6 cases had the mass resolved.

Table VI also indicates the status of the pelvic mass when the patients were discharged from the hospital. In one case there was no change. In 47 patients, the mass was smaller and in 6 patients there was, apparently, complete absorption of the mass. Five patients were discharged after operation. Two of these were mistakenly operated upon for ectopic pregnancy but laparotomy revealed acute salpingo-oophoritis with exudate. The inflamed adnexa were not disturbed and treatment was begun after the operative wound was healed. Three patients received treatments and were operated upon before leaving the hospital.

Table VII indicates the follow-up period of both hospital and clinic cases which varied from three months to more than two years. No patient was discharged from follow-up until she was asymptomatic or referred to the hospital for operation. In the course of the follow-up, 4 hospital and 5 clinic patients developed reinfections or exacerbations of the inflammation after complete subsidence of the original infection.

The marked degree of disability accompanying and following pelvic inflammatory disease is indicated in Table VIII. Only 8 patients were asymptomatic on discharge from the hospital. As seen in Table VIII, it required eighteen weeks for 90 per cent of the hospital patients to become asymptomatic. Of the less severe clinic cases, 92 per cent were asymptomatic within eighteen weeks. Two of the hospital and three of the clinic patients were classified as failures. (The two hospital patients were re-admitted and operated upon for residual masses. The three clinic patients who had persistent adnexal masses are described below, Cases 16C, 17C, and 33C.)

In Table VIII, it will be noted that in 89 per cent the sedimentation rate was normal on discharge from the hospital, or became so within four weeks. The sedimentation rate was normal in 92 per cent of the clinic patients on admission, or became so within four weeks after starting treatment. Sedimentation rate determinations were done weekly on all clinic patients.

Sterility often follows acute inflammation of the pelvic organs. In our group, 78 patients (83 per cent) had obstruction of the tubes; 63 found closed by insufflation test and 15 at operation. Fifteen patients were found to have at least one open tube, 7 determined by insufflation test, and 8 verified by subsequent pregnancy. Twenty per cent of the patients had more than one insufflation test. Insufflation tests were not done until the patients were afebrile, had normal sedimentation rates, and there was no adnexal tenderness. There were no exacerbations following insufflation of the tubes.

Final Results

Of the 94 patients studied, 76 (80 per cent) had complete subsidence and resolution of the inflammatory mass at the end of the follow-up period. Eighteen patients (20 per cent) still presented a pelvic mass; 11 of these were in the hospital group, 8 being considered of inflammatory origin, and 3 were diagnosed as ovarian cysts. Of the 8 patients

A NEW TREATMENT FOR INTRACTABLE PRURITUS VULVAE

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THIS is a preliminary report concerning 15 cases of intractable pruritus vulvae.

At the Cook County Hospital gynecologic out-patient clinic where thousands of cases are seen annually, intractable pruritus vulvae has been a distressing and annoying disorder, both to the patient and to the doctor. We see all types of pruritus vulvae, those due to chronic irritating discharges, genital atrophy, etc.; but the intractable type offered a real challenge to the clinician as to therapy and its effects. Prior to this new treatment, we have employed the usual medication, dyes, ointments, radiation, etc., but without any real benefit to the patient.

This series of 15 cases was begun in June, 1942. We present the case histories of some of these.

The solution used for injection consists basically of an anesthetic (procaine 2 per cent), benzyl alcohol (5 per cent) and a vehicle which may be olive oil, peanut or almond oil. It may be warmed to make the injections easier and thereby use a thinner needle.

The technique of injection is as follows:

The pubic and vulvar hair is not shaved. The vulva is cleansed with green soap and flushed with water. Alcohol is not used because it will cause too much burning. We have had no infections with this technique. The injection is made in four directions, along the length of the labia majora and minora on both sides, across and above the area of the clitoris, and across the lower portions of the vulva above the anal region. One-fourth inch away from the usual inflamed border laterally, the needle (21 gauge, 2 inch or spinal) is introduced at the upper pole of the labia and is carried down to the lower pole before injection of the oil is actually begun. When the point of the needle is felt at the lower angle, then the oil is injected and the needle gradually withdrawn upward until the upper pole of the labia is reached. The injection is made fairly deep into the fatty parts of the labia. Five cubic centimeters are used for each labium laterally: 2.5 c.c. for the upper and lower injections. Occasionally one may puncture a vein and develop a hematoma; although it is not a serious complication.

It will be noted that in from three to seven days the subjective symptoms are markedly diminished, or have completely abated, and the patient is relieved.

The vulva, especially the labia majora, will present slight tumefaction, of a fibrous consistency and only slightly tender. The swelling usually recedes within a week and there remains a smaller fibrotic cordlike structure for from two to four weeks. We have seen no sloughing in any of our cases, probably due to the fact that the subcutaneous tissue alone is

be that by determining whether the patient has a fairly normal tubal contractility curve, a preoperative prognosis can be arrived at with some degree of assurance. It is to be hoped that this aspect of the problem will be thoroughly investigated in the future.

The bovine allantoic membrane used in this work was furnished by Lewis Manufacturing Company, and is marketed as "Curity" Insultic Membrane.

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1. Gempfert, J. R.: AM. J. OBST. & GYNEC. 38: 256, 1939.
2. Greenhill, J. P.: AM. J. OBST. & GYNEC. 33: 39, 1937.

Discussion

DR. FREDERICK C. HOLDEN.—Those of us who were fortunate enough to hear Dr. Gempfert give his original presentation here several years ago realize that he did a lot of animal experimentation before operating upon the human subject. During the course of that work, the doctor was able to develop a refinement of technique that made it possible for him to do this operation as well as he does it at this time. It is to be expected that following any salpingoplasty, the number of patients who become pregnant is much smaller than the number of cases where tubal patency is achieved. Very likely this is due to the fact that in many cases the cilia are destroyed and propulsion of the egg is impossible. I have done the Sovak operation for tubal occlusion several times with only one successful pregnancy and that was in a case of tubal occlusion at the fimbriated end following an acute appendicitis with a postoperative pelvic abscess. In this case the tubal mucosa was apparently left intact.

I have used the Gempfert technique and in both instances I failed to obtain patent tubes.

DR. GEPFERT (closing).—I am, of course, disappointed that a higher percentage of pregnancies did not result from the described procedure. Those of us who have worked with this particular surgical agent, if I may call it that, have felt that it holds great promise. It has been used extensively in neurologic work and has gained considerable favor as a means of covering the brain to prevent formation of adhesions following brain surgery. It has likewise elicited a favorable reaction as a result of its use in reconstruction of nerves, tendons, and joints.

We feel that any substance, which is as innocuous as this seems to be, is an ideal agent to place in the Fallopian tube to maintain patency until the processes of healing have been completed. It is the very basis upon which this whole tubal reconstructive operation is built. In my opinion it has a bright future in this type of surgery. I firmly believe that as we become more discerning in our selection of patients to be operated upon, and as our surgical technique in this particular type of surgery improves, that the favorable results obtained will make a more pleasing picture.

CASE 3.—(C40-20742.) Mrs. L. D., aged 64 years, gravida vi, para vi, had had itching about the vulva for two years. Menopause in 1911. This patient had a very severe vulvar dermatitis, fissures, and lichenification. She received her first oil injection on June 3, 1942, which relieved her symptoms a great deal; however, it was deemed advisable to give her a second injection. This was done two weeks later. She made excellent progress and when last seen on Nov. 25, 1942, she had no complaints referable to the vulva.

CASE 4.—(C417878.) Mrs. C. S., aged 45 years, gravida 0, para 0, was referred from the Skin Clinic because she did not respond to the treatments. She too had an extensive involvement of the labia. She required 2 injections: first given on Sept. 22, 1942; she improved. Second given Oct. 14, 1942; she developed allergic reaction which disappeared in several days.

Last seen on Nov. 25, 1942. No complaints.

CASE 5.—(C4014-446.) Mrs. C. W., aged 42 years, had had marked pruritus vulvae for five years. She was given an oil injection on Oct. 7, 1942. She was last seen on Nov. 25, 1942, and was asymptomatic.

The other ten cases are of similar nature; all were greatly improved or completely cured.

Comments

The above described procedure is simple, practical, and is done in the office or clinic. It requires no intricate apparatus, medicines, or assistance. The patient is not incapacitated. It carries no risks or any complications, and the results are most gratifying.

UTERUS DIDELPHYS WITH ENDOMETRIOSIS*

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(From the Gynecological Service of Columbia Hospital)

THE incidence of congenital malformations of the female genital tract is undoubtedly much more common than is generally appreciated. Many of the abnormalities resulting from defective development of the reproductive organs are discovered only during the course of exploratory laparotomies in undiagnosed ailments or during the course of abdominal sections performed for conditions other than complaints arising from malfunction of the genital apparatus.

A. M., aged 16 years, unmarried, first presented herself on Aug. 18, 1941, with the sole complaint of severe dysmenorrhea ever since the onset of her menses two years ago. Except for commoner childhood diseases, her past history was unimportant and the family history irrelevant. Menses began at fourteen and had been irregular since the onset, occurring at thirty-three- to forty-two-day intervals and lasting seven to eight days with a six months' period of amenorrhea last year. Pain had been present throughout each period, from the establishment of catamenia, but had grown steadily more severe until all medications and

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injected and not the skin. Occasionally a severe case may require a second injection. Only one-half of the original amount is used and this should be carried out not sooner than two to three weeks after the first.

There was one case of allergic (oil?) cutaneous reaction which extended to the lower abdomen. It disappeared within a week. We also recommend warm baths and washing the vulvar parts with soap and water after the injections are given. This will aid in eliminating the secondary infection which is so often present prior to the treatment and is due to scratching.

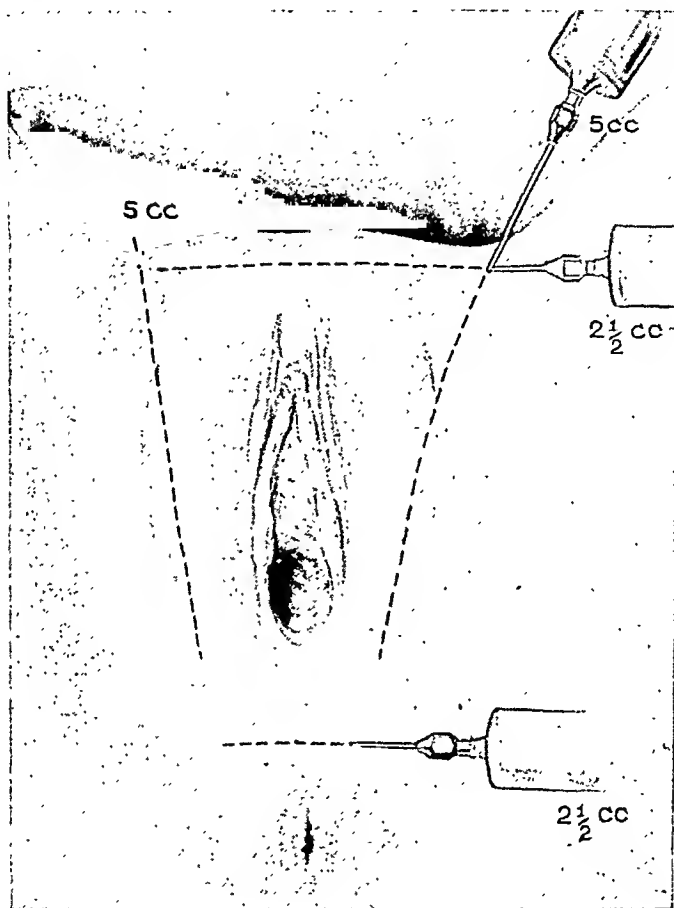


Fig. 1.

Case Reports

CASE 1.—(C4214803.) Mrs. O. P., aged 38 years, who had had pruritus vulvae since 1926. She visited various dermatologic and gynecologic clinics, but without results. She was given one injection on Aug. 14, 1942, and was seen last on Nov. 25, 1942. *No complaints*: "This is the first time in all these years that I have no itching."

CASE 2.—(C40-24435.) Mrs. A. G., aged 53 years, gravida iv, para iv, menopause at 46 years, had had burning and itching of the vulva for two years. This patient also had the usual medicaments prescribed and applied, but no effect. One oil injection on June 17, 1942, and was last seen Nov. 25, 1942. *No complaints*: "I feel wonderful," is the patient's comment.

cul-de-sac. Each uterine body had one sacrouterine ligament attached and between these ligaments were four bluish red nodular masses attached to the peritoneum. These peritoneal masses were ligated and excised. The right uterus, tube and ovarian cyst were removed. The left uterine structure, with its appendages, was brought to the midline and suspended by utilizing the right broad and round ligaments.

Pathologist's Report.—The specimens consisted of a uterus, tube, ovary, and appendix. The uterus weighed 44.2 Gm. and measured 5.5 by 4.5 by 3.5 cm. It appeared to have a cervix but no outlet could be found. The uterine cavity was of normal size but had no outlet through the rudimentary cervical structure. The ovary measured 7 by

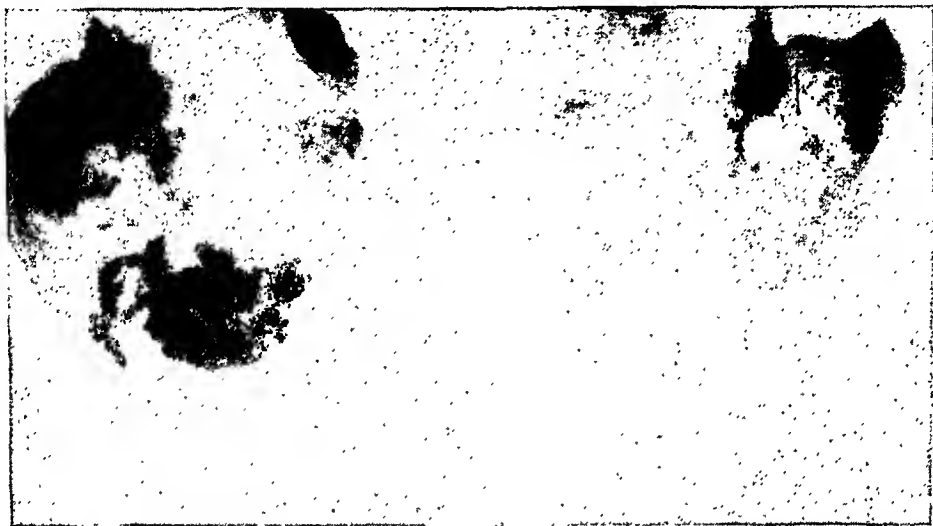


Fig. 1.—An injection of 5 c.c. of opaque medium into the uterine cavity shows an abnormal appearance suggesting one side of a uterus didelphys. Left tube patent. removed before the photograph was taken.

15 cm. and was made up of a collapsed cystic cavity which had been previously opened (or ruptured) at the hilum. Lining of cavity was smooth and congested with old blood. Also presented were four small cystic structures containing old blood.

Histologic Examination.—There were normal uterine structures; endometrium thick with irregular glands, filled with secretion. Sections of ovary revealed several follicular cysts and one large corpus luteum cyst. The small pieces of tissue from the pelvis revealed numerous endometrial glands filled with blood and surrounded by some stroma. The appendix showed very little fat replacement in the submucosa but considerable fibrous tissue. One small area of thickened serosa contained two cysts which were lined with fairly tall cells suggesting endometrium, but one could not definitely state that they were endometrium.

Diagnoses.—(1) Uterus, well developed except for rudimentary cervix. (2) Follicular and corpus luteum cysts of ovary. (3) Peri-oophoritis. (4) Endometriosis, pelvic peritoneum. (5) Peri-appendicitis. (6) Endometriosis, appendix.

This young girl made an uneventful, afebrile convalescence and left the hospital on her twelfth postoperative day. An examination made

therapy, short of opiates, had failed to bring relief. During the past year she had lost four or five days from school during each period and was confined to bed most of that time. This monthly incapacity had caused misery and fear which had interfered noticeably with the girl's morale, and had resulted in capricious eating habits.

Physical Examination.—Patient was a tall (66 inches), rather thin young girl weighing 115 pounds. Voice was feminine in type. Eyes, ears, nose, and throat were normal. Breath was fetid. Hair distribution was normal. The breasts were moderately well developed. Heart and lungs were normal. The abdomen was flat and there was no rigidity; no spasm or masses were elicited. There was, however, slight tenderness on deep palpation in the right lower quadrant.

The external genitals were normally developed and the hymen intact with a small irregular aperture. Rectal examination suggested the presence of a small globular mass in the right adnexal area and a less well-defined ovoid mass to the left. The uterus could not be ascertained in the midline but the structure lying well to the left of the midline, and having more the consistency of the uterus, suggested the possibility of some unusual pelvic pathology and examination under anesthesia was advised.

On Sept. 13, 1941, the patient was examined under ethylene anesthesia after first incising the hymen. The cervix was visualized, in a normal vagina, lying to the left of the midline and pointing toward the right side. Palpation revealed a firm, elongated structure extending upward from the cervix and toward the left pelvic wall and a similar, though rounder, structure on the right which did not move with the cervix.

At this point a small cannula was introduced into the cervix for the purpose of introducing lipiodal. The cannula veered off abruptly to the left when inserted. Five cubic centimeters of lipiodal were injected and x-ray plates taken. These disclosed an irregular spread of the opaque substance lying wholly in the left side of the pelvis and bore no resemblance to the usual outline of a normal uterine cavity. The procedure was considered unsatisfactory but aroused suspicion of some uterine abnormality.

The parents of the girl agreed to permit repetition of this procedure at some future date. This was done on June 22, 1942, and a more satisfactory filling with lipiodal was obtained. Once again the shadow was seen only in the left side of the pelvic cavity, but it was more elongated and was interpreted as representing the uterine cavity with a single patent tube. Exploratory laparotomy was advised.

Laboratory Data.—Urine was negative except for a few epithelial cells. Blood count showed 4,630,000 erythrocytes, 9,400 leucocytes, and 78 per cent hemoglobin. Wassermann was negative.

Operation.—On July 22, 1942, the abdomen was opened through a midline suprapubic incision and two uteri of equal size were found. The left uterus, attached to the single cervix seen in the vagina, bore a normal tube with a normal ovary in the usual position. The right uterus, attached to its mate only by a thickened fibrous band in the region of the internal os, bore a relatively normal tube which was spread out and densely adherent to a thin-walled cyst of the right ovary. No cervix could be found but the uterine structure tapered off into a blind end in the fibrous connecting band. The uterine bodies were freely movable and could be elevated separately or spread widely apart to expose the

BILATERAL ADENOCARCINOMA OF FALLOPIAN TUBES

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THE patient was a 46-year-old, colored female admitted to the gynecologic ward of Grady Hospital on July 24, 1942. She delivered twins in 1917, and was operated upon thirty years ago for "female trouble." Her chief complaint was "frequent menstrual discharge and a tumor in the abdomen." She menstruated regularly until seven months ago when metrorrhagia began. The discharge was thin, profuse, and rust colored. She was first seen in May, 1942, and was told that she had a tumor of the uterus and was advised to return for admission to the hospital.

The patient was a well-developed obese woman. The blood pressure was slightly elevated and a firm nodular mass filled the lower abdomen. Laboratory and roentgen ray studies were essentially negative. Abdominal hysterectomy done.

Pathologic Examination.—The uterus was large and asymmetrical. The cavity was distorted by two large intramural fibromyomas. The endometrial lining showed some thinning due to the fibromyomas and was proliferative in type, and showed no neoplastic change.

Fallopian Tubes.—Both tubes were covered by several fibrohemorrhagic adhesions. The outer two-thirds of each tube was dilated and had a retort shape. They were fairly tortuous and heavy. In the distal one-third of the left tube was found a large cystic cavity measuring approximately 4.5 by 5 cm. in diameter which had produced some thinning of the wall. The cavity contained soft red partially clotted blood and a few small grayish soft necrotic masses of tissue. The lining of the cavity was irregular. The right Fallopian tube was approximately the same size and measured 8 cm. in length. The ampullar end was adherent to the ovary. On section this tube contained the same type material found in the left tube. The wall of this tube was markedly thinned. The middle one-third was almost solid and was filled with grayish, soft, neoplastic tissue. The medial one-third measured 0.8 cm. in diameter, appeared to be occluded and was sharply demarcated from the middle one-third. On microscopic examination both tubes were essentially the same except the wall of the left tube was invaded from the inside by islets of neoplastic cells. Some of these islets contained acini and some were composed of sheets of neoplastic cells. Section of the soft grayish contents of the lumen revealed a papillary arrangement of neoplastic tissue with loose fibrous stroma. The acini were lined by low columnar epithelium with darkly staining nuclei. There were several mitotic figures and the cells varied in size. In the right Fallopian tube there was thinning of the fibromuscular wall without neoplastic infiltration. In one area was seen what appeared to be a growth of papillary projections from the mucosal lining. These papillary projections were covered with low columnar epithelium which contained many mitotic fig-

at the office, two weeks after her release from the hospital, showed the uterus to be in good central position in the pelvis and reasonably mobile. She was permitted to return to school five weeks after operation. Three menstrual periods have occurred in twelve weeks that have elapsed since operation, the first of which began on the ninth postoperative day. There was mild cramping with this period which was relieved by two administrations of one-half gr. of codeine phosphate. The last two periods have been without discomfort and have proceeded without curtailment of school or other activities.



Fig. 2.—Schematic and actual reproduction of pathology as sketched at operating table.

Summary

1. The diagnosis of some abnormality of the internal generative organs was aided by uterosalpingography.
2. Exploratory laparotomy revealed the presence of a double uterus (uterus didelphys), ovarian cyst, and endometriosis of the pelvic peritoneum.
3. Extirpation of the rudimentary uterus, ovarian cyst, appendix, and peritoneal endometrial implants was performed.
4. The transtubal implantation theory of endometriosis (Sampson) might seem tenable in this case.
5. There has been no dysmenorrhea in the three menstrual periods which have occurred since operation.

Discussion

The purpose of this report is to report another case of primary adenocarcinoma of the Fallopian tube and to direct attention to the increasing number of cases reported in the recent literature. Robinson¹ states that the first case of primary cancer of the Fallopian tube was reported by Renaud in 1847, and Rokitsansky gave the first pathologic description in 1861. The majority of authors give priority to Orthmann who described the condition clinically in 1886.

Incidence

Martzloff,² in 1940, stated that, according to various estimates in the literature, the incidence of primary tubal cancer ranges from 0.34 per cent to 1.35 per cent of operations on diseased tubes. He also cites 392 cases up to 1938. Thirty-five additional cases are tabulated in the *Cumulative Index* in both foreign and domestic literature up to July, 1942. This brings the approximate number of cases to 427.

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VASA PREVIA

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THE rather infrequent pathologic condition of velamentous insertion of the umbilical cord is defined as the separation of the vessels of the cord some distance from the placental margin, with the arteries and veins making their way to the placenta through a fold of amnion. When the velamentous vessels are inserted low down in the uterus, they may extend across the internal cervical os giving rise to the anomaly known as vasa previa, an apparently rare but, nevertheless, clinically important condition. The literature on the subject of velamentous insertion of the cord reveals occasional case reports,¹⁻⁴ while that on vasa previa is practically non-existent. A case of vasa previa is herewith presented because it embodies the unusual in pathology together with a medical paradox in that a mistaken diagnosis probably indirectly resulted in the delivery of a living child.

Mrs. D. W., aged 23 years, gravida ii, entered Firmin Desloge Hospital on Sept. 12, 1942, complaining of vaginal bleeding of one hour's duration. Her last period was on Jan. 31, 1942, with her expected date of confinement estimated to be Nov. 8, 1942. The bleeding, which was painless but quite profuse, lasted for about fifty minutes after entrance into the hospital. She was immediately put to bed and given morphine gr. $\frac{1}{4}$ hypodermically. A probable diagnosis of placenta previa was made at this time. The bleeding stopped entirely and did not recur but the patient was kept in bed throughout the remainder of her prolonged hospital stay. On admission, the red blood cells were 3,600,000 and the

ures. The stroma resembled that of the mucosal folds of the normal tube, but was decreased in amount. These papillary projections were growing centripetally from the mucosal lining and were closely crowded together in the lumen. The lining epithelium was 2 to 4 cell layers in



Fig. 1.—Cross-section of Fallopian tube showing: *a*, thinned serosal covering and part of muscular coat; *b*, replacement of submucosa and muscular wall by papillary-shaped adenocarcinoma; *c*, papillary projections of neoplasm filling the lumen and replacing the mucosa. Approximately $\times 160$.

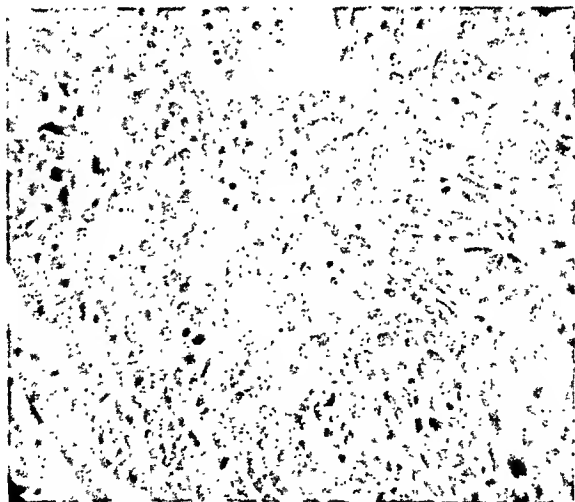


Fig. 2.—Neoplastic papillary growth with enlarged cells containing hyperchromatic nuclei, mitoses and pseudoacinous formation. Approximately $\times 400$.

thickness. In areas where the papillary projections were cut at right angles an acinar appearance was simulated. This process represented about a Grade II papillary adenocarcinoma.

The ovaries contained ample follicular cysts and showed no evidence of malignant change.

with residual inflammatory masses, 7 were operated upon. One had a hydrosalpinx, and 6 had tuboovarian abscesses, sterile on culture. The postoperative course was uneventful in all cases. Of the 3 ovarian cysts, one was verified at operation, the other 2 patients were not operated upon, being asymptomatic. Of the 7 clinic patients with residual masses, 5 were believed to be of inflammatory origin and 2 were ovarian cysts. Of the 5 inflammatory masses, only one patient consented to operation, an old hematosalpinx being found.

In addition, 3 clinic patients who were asymptomatic came to operation. The diagnosis in these cases was uterine fibroids with pelvic exudate. These patients were operated upon after the exudate had been completely absorbed by treatment. Operations revealed evidence of the old tubal infection, but adhesions were easily broken up and the uterine tubes were removed without difficulty. These patients had uncomplicated post-operative courses.

Details of Cases Operated on for Residual Inflammatory Masses

Patients Operated Upon With Persistent Pain and Pelvic Mass.—

1. M. H. (Case 20), colored, aged 43 years, gravida 0, had large bilateral pelvic masses. After 15 treatments, she was discharged to the clinic, where she received 24 additional treatments. At the end of three months, the masses were smaller, but patient still complained of pain and sedimentation rate was still rapid. While waiting readmission for operation, she had a severe acute exacerbation during a menstrual period. After 21 more treatments in the hospital, operation revealed a huge tuboovarian abscess 15 cm. in diameter on the left side. The right was three times normal size, fixed, but contained no pus.

2. J. J. (Case 26), white, aged 38 years, gravida 0, was found to have bilateral adnexal masses. After 16 treatments, she was discharged to the clinic, given 18 additional treatments and followed for seven months. The mass on the left was completely absorbed, but the mass on the right had shown no change for the last four months under observations. Because pain persisted, patient was operated upon and a right hydrosalpinx 5 cm. in diameter was found. The left tube was thickened and fixed.

Patients With Persistent Inflammatory Mass but Asymptomatic.— There were 6 patients (Cases 19, 21, 22, 30, 34, and 21C) who were given a variable number of treatments in the hospital and in the clinic, and were then operated upon because the pelvic masses had not been completely absorbed. These patients, at the time of operation, were asymptomatic and had normal sedimentation rates. In five instances, unilateral or bilateral sterile tuboovarian abscesses were found, and in one case an old hematosalpinx was present.

TABLE IX

TOTAL	PATENCY OF TUBES			
	Closed		Open	
94	Insufflation Test	Verified by Operation	Insufflation Test	Verified by Pregnancy
Hospital (54)	33	11	4	6
Clinic* (40)	30	4	3	2

*One clinic patient not tested. Developed a re-infection before insufflation test could be done.

hemoglobin, 9.8 Gm. The following day a 1,000 c.c. bank blood transfusion was administered. During the ante-partum hospitalization, from September 23 through October 27, the patient received corpus luteum hormone, as recommended by Falls and others.⁵ Three ampoules of lutein were given three times daily for twenty-one days after which the dosage was reduced to two ampoules three times daily. Also, three separate cystograms were made. On September 14, air was injected into the bladder and an x-ray picture taken. This, however, provided no definite information. On September 17, sodium iodide was injected into the bladder and the resultant picture was suggestive of placenta previa marginalis. A third cystogram was made on October 27, using sodium iodide solution and again a quite definite diagnosis of a marginal type of placenta previa could be made from the x-ray film. Without further study cesarean section was decided upon and performed on Oct. 28, 1942. The operation was a classical type of section, this particular case being unsuited to the low cervical procedure because no lower uterine segment had developed. The uterus was incised high in the body, the incision carrying down directly through placental tissue and, thus, immediately refuting the preoperative diagnosis. A living male infant was extracted without difficulty. The placenta was then manually separated from the uterine wall and a typical velamentous insertion of the cord was noted. Large vessels in the amnion were located deep in the lower uterine segment and these covered the entire internal os. The placenta was removed in toto, the remainder of the operative procedure being brought to its conclusion in the routine manner.

This case presented many of the signs and symptoms of a rather typical placenta previa. Such a diagnosis was tentatively made because of the painless bleeding occurring in the last trimester of pregnancy. Cystograms tended to corroborate the diagnosis. Vaginal examination was not done simply because we believed our findings to be fairly conclusive. The case was treated as a placenta previa and massive doses of lutein, bed rest, sedation, and transfusion were prescribed. At operation, of course, the presumptive diagnosis was swiftly ruled out by incising placental tissue after entering the uterine cavity high in the fundal area. It is noteworthy that the failure to perform a vaginal examination prior to operation doubtless indirectly saved this infant's life. Had such an examination been carried out, the palpating finger would not have contacted typical placental tissue. The diagnosis then would be refuted, cesarean section discarded, and the patient undoubtedly would be allowed to progress to spontaneous labor. The result of such a course could readily have been disastrous not only to the infant but possibly even to the mother since the velamentous vessels conceivably could be torn at the time of rupture of the membranes with resultant severe hemorrhage, death to the fetus plus certain embarrassment to the mother. Such was the case in three instances of spontaneous rupture of the vessels with the deaths of two babies as reported by Caffaratto.⁶ Finally, the picture of placenta previa obtained by cystogram studies was probably produced by the presenting umbilical cord and placental vessels.

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METROPOLITAN BUILDING

INTESTINAL TISSUE IN THE UMBILICAL CORD

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AS THE umbilical cord is formed by the fusion of the allantoic stalk with part of the vitello-intestinal duct and the remains of the yolk sac, it might seem probable that intestinal tissue would, not very infrequently, be found in the umbilical cord (a misplaced Meckel's diverticulum?). No mention of this condition, however, has been found in any of the considerable number of works on obstetrics and gynecology which have been consulted. While no careful search of the literature has been made, the finding of intestinal tissue here appears rare enough to warrant a brief report of such a case.



Fig. 1.—Showing the piece of intestinal tissue in the umbilical cord. Wharton's jelly which filled the space between this and the convex portion of the cord was partly removed before the photograph was taken.

A 19-year-old primipara gave birth to a full-term infant by spontaneous delivery. It was noted at the time of delivery that near the midportion of the umbilical cord there was a mass the size of an orange, ovoid in shape. On cutting through the outer part of this, there was some jelly-like substance, and also an elongated brownish structure about 6 cm. in length which was thought to be suggestive of a teratoma.

As received at the laboratory, the placenta showed no pathology. The umbilical cord was attached a short distance from the center. The cord measured 35 cm. in a straight line from end to end, but was longer than this because of a large bowing at one part. The first 20 cm. from the placenta was of medium size with the usual twists. Then came the bowing in the cord, about 8 cm. on the straight edge and 13 cm. around the convex portion. The cord was much thicker along this convex portion than it was at either end due to the thickness of Wharton's jelly, which was so transparent that the umbilical vessels could be readily followed by transmitted light. They were larger here than elsewhere. The concave portion of this bow was filled by Wharton's jelly which had separated into two layers, forming the cystlike space from which the mucoid material came at the time of delivery.

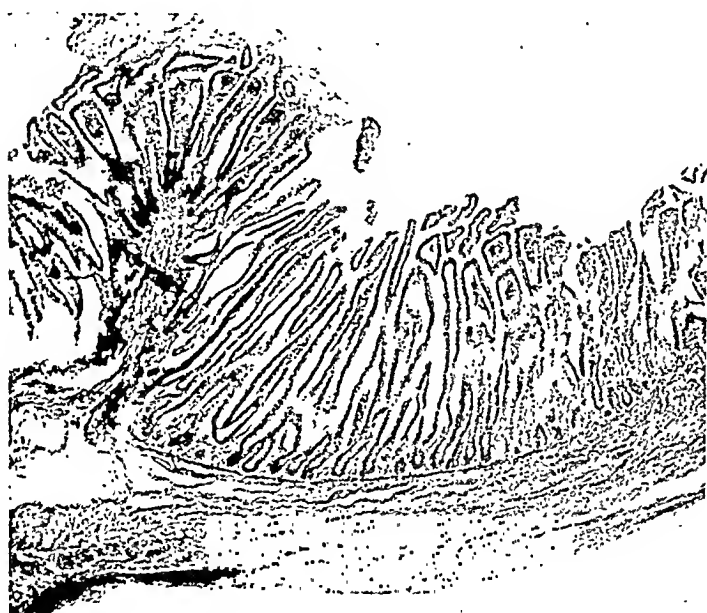


Fig. 2.—Section showing intestinal tissue in the umbilical cord.

Lying in the Wharton's jelly along the straight edge of the bow was a reddish brown structure, extending lengthwise of the cord (Fig. 1). This measured about 6 cm. in length and nearly 2 cm. in transverse diameter, tapering somewhat at the ends. It was a little irregular on the surface. On removing a small portion of this near the center it was found to have a lumen containing a brownish amorphous substance. Microscopic examination of this piece showed the structure of small intestine including all of the layers of the intestinal wall (Fig. 2). A small portion taken from near each end showed a similar structure. On opening the specimen lengthwise the lumen was found to extend the entire length but was closed at each end.

If this intestinal structure had been on the other side of the umbilicus, it presumably would have formed a Meckel's diverticulum.

CORNUAL PREGNANCY

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(From the Gynecological Department of the Sinai Hospital)

IT HAS been observed that of the various forms of ectopic pregnancy, the interstitial or cornual variety is the most infrequent. In a study of 1,547 cases of ectopic pregnancy, Wynne observed 18 cases or a percentage of 1.16. Rosenthal found 3 per cent of 1,324 cases of ectopic pregnancy and Weinbrenner collected a total of only 35 in several thousand cases. Kelly, in *Operative Gynecology*, quotes Martin as having seen only one in 75 cases, and the author, in several thousand cases, has never seen an example of this particular type of ovarian pregnancy.

Schuman's complete study of the subject as written in his monograph *Ectopic Pregnancy* reveals three cases of his own. His observation from perusal of the literature is that most cases present themselves on the posterior surface of the uterus. However his three cases were on the anterior site.

Following is a report of the history, physical, operative and pathologic findings of an unruptured interstitial pregnancy.

This patient, S. G., aged 31 years, was seen on Dec. 6, 1942, with the complaint of vaginal bleeding and lower abdominal pain of fifteen days' duration.

The patient had been married for seven and one-half years, and despite the fact that she had attempted to become pregnant for six and one-half years, her efforts had proved to be fruitless. The family, past, and systemic histories were entirely irrelevant. Her menses began at the age of 13 years, occurred regularly every twenty-eight days, and lasted for three days, with only a moderate flow. There was severe back pain the first day of the period. The last regular period occurred on Oct. 23, 1942. This lasted the usual three days. On November 21, the date of the next expected period, the patient began to bleed again. However, on this occasion the bleeding persisted.

The physical examination revealed a well-developed white female, not in acute distress. The breasts were moderately enlarged but no colostrum could be expressed. Abdominal examination elicited no spasm, rigidity, or tenderness to palpation. The pelvic examination was not remarkable. There was a scant bloody discharge. The cervix was soft; the uterus was in anterior position, regular, and suggestive of slight symmetrical enlargement. The possibility of intrauterine pregnancy was considered and a Friedman test proved to be strongly positive.

The patient was treated conservatively. She was confined to bed and observed for further pain and bleeding. Twenty-one days after the onset of the November period (December 12) the bleeding became more profuse and was associated with severe lower abdominal cramplike pains. Hospitalization was advised and she was admitted with a provisional diagnosis of incomplete abortion. Two days later, on December 14, curettage was performed and a small amount of tissue was removed from the uterine cavity. The pathologist reported: "fragments of degenerated decidual tissue; no fetal villi."

Postoperatively, there seemed to be no subsidence of symptoms. The lower abdominal pain and vaginal bleeding persisted. On several occasions there were questionable spasm and rebound tenderness in the lower right quadrant. At one phase of her illness there was an elevation of temperature to 102° F. The white blood count was 12,000 polymorphonuclear leucocytes. Hemoglobin was 80 per cent and the red blood count was 4,500,000 cells. The temperature subsided in two days, but the pain and vaginal bleeding continued. Under sterile precautions, a pelvic examination failed to reveal any adnexal masses.

Five days later there was an acute episode of severe lower abdominal pain. The patient also complained of faintness and pain in the shoulder. Spasm, tenderness, and rebound tenderness were present in the lower right quadrant, but the patient gave no evidence of being in shock. It was thought advisable, because of these symptoms and signs, to perform a laparotomy.

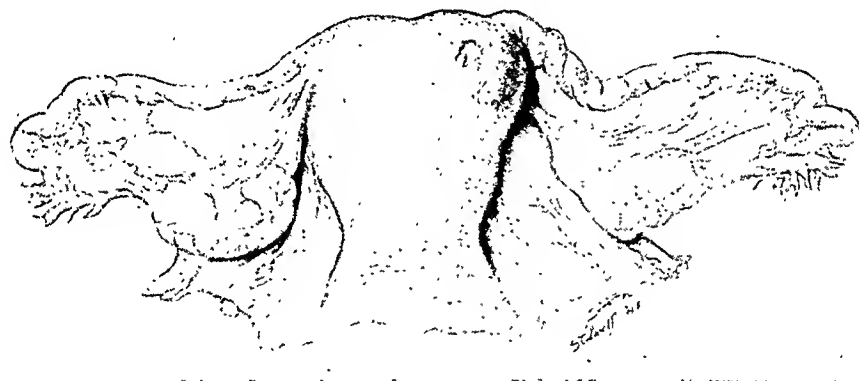


Fig. 1.

Under anesthesia, prior to operative procedure, another pelvic examination was done. This time a small nodular mass was found extending from the right posterior fundal portion of the uterus.

At operation, no blood was seen in the peritoneal cavity. The right tube was injected and edematous. The right ovary was normal, as were the left tube and ovary. The uterus was slightly larger than normal. On the posterior surface at the cornual angle, there was a mass the size and shape of a marble. The top of this mass seemed to form an apex, was blue in color, and apparently at the point of rupture. This portion of the uterus and the right tube were removed.

The pathologic report revealed a cornual pregnancy and chronic salpingitis.

Except for slight abdominal distention and elevation of temperature in the first week postoperatively, the recovery was uneventful.

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A NEW ABDOMINAL BINDER FOR INTRA-PARTUM USE

Preliminary Report

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IN 1924, "the almost forgotten abdominal binder" was revived and added to the obstetrician's armamentarium. Prior to this time, the primary use of the obstetric binder was as an ante-partum support in abdominal wall weakness and was only secondarily employed in such cases during labor. Beck demonstrated the effectiveness of a binder specifically designed for use in the intra-partum period only. However, all binders in use are modifications of a simple corset, designed to compress the abdominal cavity and thus exert pressure, indirectly, on the

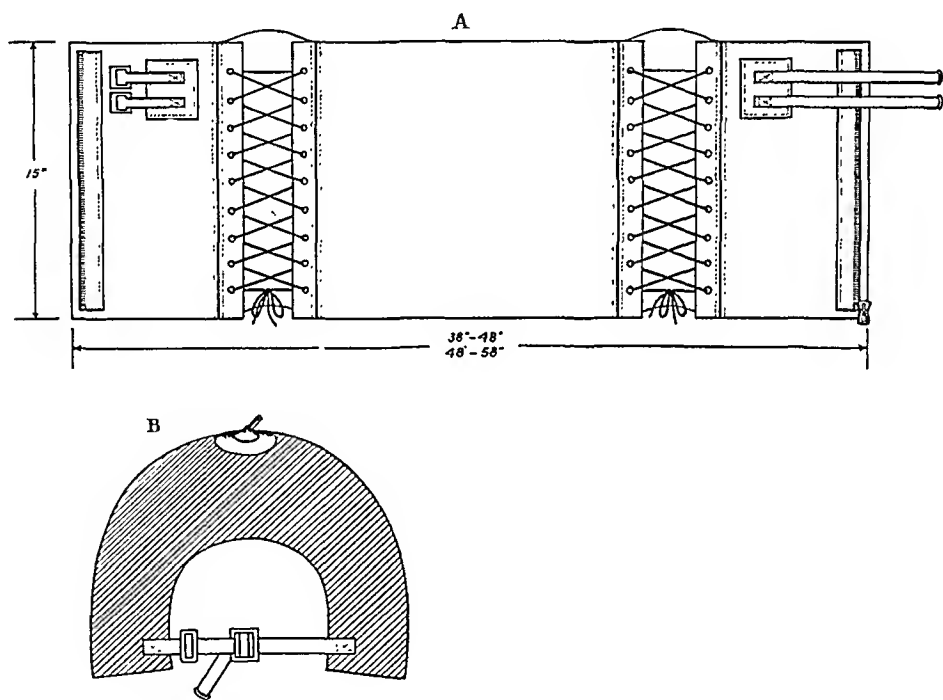


Fig. 1.

uterus and its contents. The greater pressure thus required produces a high degree of discomfort and occasionally difficulty in respiration. To overcome these objections and to increase the effectiveness of pressure directly on the uterus, the author has designed the binder described below, which is now in trial at the Beth-El Hospital.

The binder consists of two distinct parts. The outer jacket (Fig. 1, A) is made of strong canvas, measures 15 inches in width and has a variable and adjustable length of from 38 to 48 inches. The adjustments (to meet individual differences) can be made by lacings on both

sides. A larger jacket, frequently necessary, from 48 to 58 inches in length, is also available. The entire front can be quickly closed by a full length zipper. The inner part is an inflatable, horseshoe-shaped, canvas covered rubber tube (Fig. 1, *B*) which is placed about the fundus and sides of the uterus (Fig. 2). The adjustable cross strap is to limit the lateral expansion of the tube, when inflated.

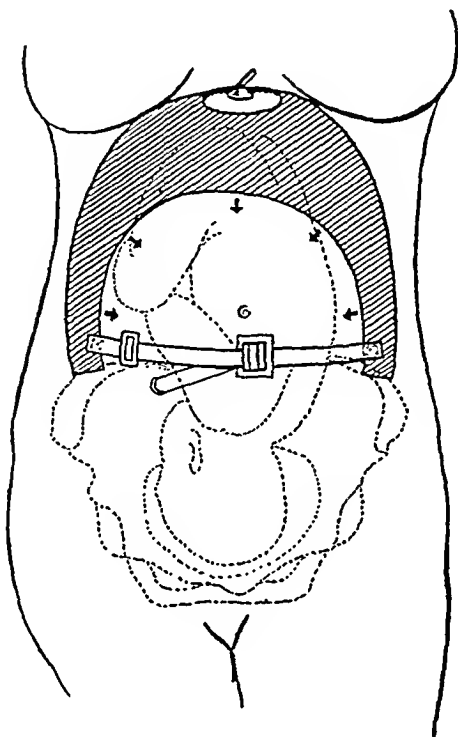


Fig. 2.

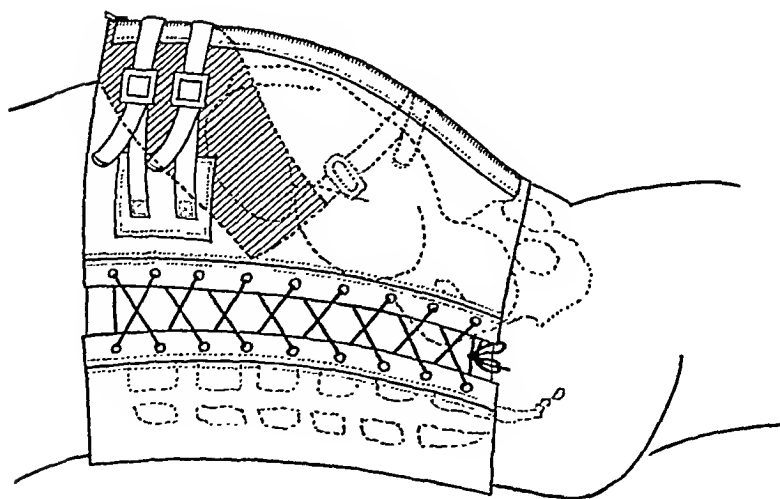


Fig. 3.

In using the binder, the outer jacket, of suitable size, is first applied, leaving the zipper front open. The deflated rubber tube is placed over the fundus and sides of the uterus and the cross strap is adjusted. The zipper front is closed and the side laces adjusted so that the jacket is

snug yet comfortable. The inner tube is then inflated with a hand pump until the pressure attained is sufficient to produce further descent of the presenting part, without any added appreciable discomfort to the patient. Fig. 3 is a lateral view of the binder as applied.

From the foregoing description, it is obvious that this binder differs from all others in its use of an inflatable tube as the means of aiding labor. This produces the following advantages: (1) Pressure is exerted directly on the fundus and sides of the uterus; (2) this evenly distributed pressure is transmitted to the uterine contents and the presenting part is thereby forced toward the pelvic outlet; (3) as the presenting

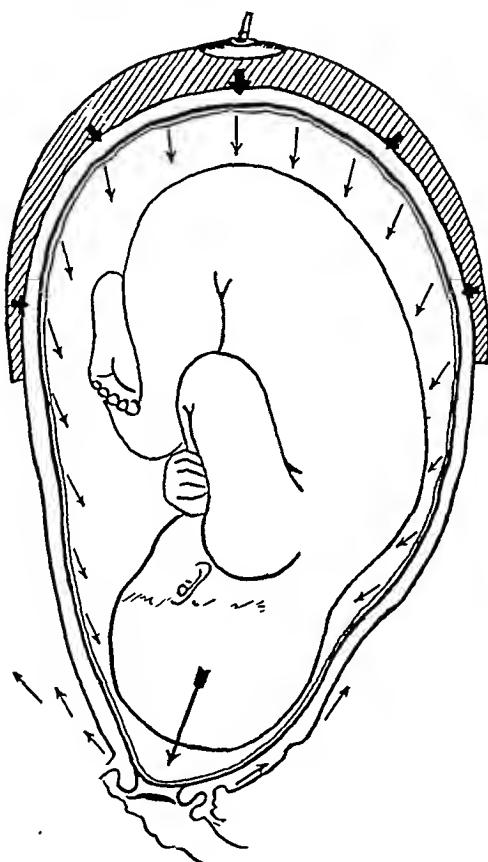


Fig. 4.

part descends, the "slack" is automatically taken up by the pressure in the inflated tube and no further adjustment of the binder is necessary, as in the case of the current binders; and (4) there is no "crawl" of the binder. Fig. 4 illustrates diagrammatically the mechanical principles involved.

Indications for Use

Consensus of opinion limits the use of an obstetric binder to the second stage of labor. Earlier application may result in premature separation of the placenta or possible intracranial injury to the fetus. In the second stage, the binder finds its greatest use in cases of malposition of the vertex, e.g., occipitoposterior, occipitotransverse, and abnormal attitudes (deflections). It is also of value in cases with normal vertex positions, associated with uterine lag or inertia due to abdominal wall

weaknesses, such as diastasis reeti, ventral hernia, thin musculature, and pendulous abdomen due to multigravidity. The binder causes further descent of the presenting part, rotation occurs, the second stage is shortened; all of which may result in a decrease in the number of operative deliveries.

A number of indications for the use of this binder, in the first stage of labor, have been suggested. For example, it may prove of value in a trial of labor in borderline cases of cephalopelvic disproportion, or in placenta previa marginalis, by forcing the presenting part against the bleeding area. However, I wish to state that I have had no personal experience with the binder in the suggested indications and therefore do not recommend its use during the first stage by anyone who has not had considerable experience with the use of binders.

The author wishes to thank Dr. M. Spiegel and Mr. B. Saxon for the drawings used in this article.

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Jones, W. N.: Gynecologic Problems of Elderly Women, South. Surgeon 10: 203, 1941.

Pyuria, senile vaginitis, prolapsus uteri, and tumors of the external genitals and vulva are the common gynecologic problems encountered in elderly women. For pyuria without hematuria the conservative therapy of rest, heat, diet, and urinary antiseptics is advocated by Jones.

In senile vaginitis we must search for a causative lesion or fungus growth. When the cause is undetermined, stimulation of metabolism of the vaginal mucosa is needed. This is best done by vitamin A administration, high vitamin diet, and daily vaginal insertion of tablets containing acidified glycogen.

The type of uterine prolapse and the degree of injury of the supporting structures dictate the choice of operative procedure. Four operations are suitable, namely: vaginal hysterectomy, the Watkins interposition operation, the Manchester parametrial fixation operation, and LeFort's colpocleisis. Often a combination of two procedures or a composite operation is the most efficacious.

Tumors of the vulva and external genitals make up the greater number seen in this group. Usually they are slow growing and well differentiated. Epithelioma of the vulva is the most common and the most favorable to excision. Surgery is the treatment of choice.

J. P. GREENHILL.

Department of Statistics

CLINICAL-PATHOLOGICAL STUDY OF THE INFANT AND FETAL MORTALITY FOR A TEN-YEAR PERIOD AT THE CHICAGO LYING-IN HOSPITAL*

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FROM the opening of the present Chicago Lying-in Hospital on May 21, 1931, until July 1, 1941, a period of approximately ten years, there have been 27,321 infants born in this institution. Included are 293 pairs of twins and two sets of triplets. During the same interval approximately 900 additional women have been patients in the hospital because of the termination of pregnancy prior to the time that birth must be reported.

The total mortality among the reportable infants† was 4.28 per cent; 614 were born dead and 559 were born alive but died before leaving the hospital. An infant was considered liveborn if the heart was beating at the time of birth, regardless of whether respiration was established.

Slightly less than one-half of the fetuses and infants were at term‡ (Table I). Although 1,000 Gm. are considered the lower limit of viability in this paper, infants weighing between 1,000 and 1,500 Gm. frequently do very poorly, and by some investigators are also considered previable. In this series almost one-third of the dead fetuses and infants weighed under 1,500 Gm.; the mortality among infants weighing more than this is 1.6 per cent from death before or during labor, 1.3 per cent from death after birth.

TABLE I. TIME OF DEATH IN RELATION TO THE PERIOD OF GESTATION

PERIOD OF GESTATION	ANTE PARTUM		INTRA PARTUM		NEONATAL		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Previable	81	7	24	2	91	8	196	17.
Premature	148	12	80	7	271	23	499	42
Term	143	12	138	12	197	17	478	41
Total	372	31	242	21	559	48	1,173	100

Post-Mortem Examination

Post-mortem examinations have been made on 81 per cent of the infants and fetuses who failed to survive. The incidence has risen from 60 per cent of the deaths

*Assistance in the preparation of these materials was furnished by the personnel of Work Projects Administration Official Project No. O. P. 665-54-3-387.

†In Illinois all liveborn infants, and all stillborn fetuses advanced to the fifth month of gestation must be reported to the local Health Department.

‡Determined by fulfilling two out of three of the following criteria; Term, 2,500 to 4,499 Gm., 47.1 to 54 cm., 38 through 42 weeks. Premature, 1,000 to 2,499 Gm., 35.1 to 47 cm., 29 through 37 weeks. Previable, 400 to 999 Gm., 28 to 35 cm., 22 through 28 weeks.

TABLE X

TOTAL					
94		Complete resolution Residual mass 11			
Final Findings: End of Follow-Up or Before Readmission to Hospital					
Hospital (54)	43	Inflammatory	8	Ovarian cyst	3
		Operated	7	Operated	1
		(Tuboovarian abscess	6)	Not operated	2
		(Hydrosalpinx	1)		
		Not operated	1		
Final Findings: End of Follow-Up or Before Admission to Hospital					
		Complete resolution Residual mass 7			
Clinic (40)	33	Inflammatory	5	Ovarian cyst	2
		(Hemato-salpinx)			
		Operated	1		
		Not operated	4	Not operated	2

Clinic Patients With Persistent Pain and Residual Pelvic Mass.—

1. B. F. (Case 16C), white, aged 22 years, gravida i, had lower abdominal pain for three weeks. On the left side, there was a firm, fixed, tender mass, 8 cm. in diameter. Sedimentation rate was rapid. Temperature was 104° F. Hospitalization was refused. She received 26 treatments, and was followed for seven months. She was never entirely asymptomatic and continued to have attacks of pain on the left side. At the end of seven months, the mass was still 5 cm. in diameter, fixed, and slightly tender. A clinical diagnosis of tuboovarian abscess was made, but patient refused operation.

2. G. D. (Case 17C), colored, aged 32 years, gravida ii, para 0, had had intermittent lower abdominal pain for six years. Bilateral masses, right 6 cm., left 5 cm., were present. Patient refused to be hospitalized and was given 17 treatments. She improved but was never entirely asymptomatic. At the end of one year, the masses were only slightly smaller. Clinical diagnosis of bilateral tuboovarian abscesses were made, but patient decided to defer operation.

3. L. F. (Case 33C), white, aged 30 years, gravida ii, para ii, lower abdominal pain, more on left, for two weeks. Intermittent pain had been present for three years. There was a cystic, fixed, tender mass, 6 cm. in diameter on left. Right fornix was tender but no mass was present. She received 14 treatments and was followed for one year. At the end of that time, the mass on the left was freely movable, slightly smaller, but still cystic. Operation was advised, but refused.

Comment and Discussion

Acute pelvic inflammation of tubal origin may present varied clinical pictures. It is obvious from our records that hospital treatment is not sufficient and that longer or shorter periods of treatment after discharge are necessary. Although all patients were afebrile for six days and ambulatory for two days before discharge, 48 of 54 patients had adnexal masses and 45 had increased sedimentation rate. Neither can we categorically prescribe a certain number of treatments with this technique. Many times we were tempted to operate upon these patients

TABLE III. PATHOLOGIC LESIONS DEMONSTRATED IN 954 AUTOPSIES IN RELATION TO TIME OF DEATH AND PERIOD OF GESTATION

TIME OF DEATH	NO. AU-TOPSY	ANOXIA		TRAUMATIC HEM-ORRHAGE		MAL-FORMATIONS		INFECTION		BLOOD DYSCRASIAS		SYPHILIS		MISCE-LLANEOUS		NO ABNOR-MALITIES		TOTAL AUTOPSIES	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Ante partum																			
Prev.	10	5		2		8		1		1		0		0		54		81	
Prem.	23	36		2		11		0		5		0		0		71		148	
Term	33	36		5		10		4		3		0		0		52		143	
Total	66	77	25.2	9	2.9	29	9.5	5	1.6	9	2.9	0	0	0	0	177	57.9	306	100
Intra partum																			
Prev.	1	3		1		3		1		0		0		0		15		24	
Prem.	10	31		5		13		0		1		0		2		18		80	
Term	33	45		24		20		5		1		0		0		10		138	
Total	44	79	40.0	30	15.1	36	18.2	6	3.0	2	1.0	0	0	2	1.0	43	21.7	198	100
Neonatal																			
Prev.	13	13		7		4		5		0		0		2		47		91	
Prem.	53	51		44		28		18		2		2		9		64		271	
Term	43	22		40		33		21		16		0		7		15		197	
Total	109	86	19.1	91	20.2	65	14.4	44	9.8	18	4.0	2	0.4	18	4.0	126	28.1	450	100
Total	219	242	25.4	130	13.6	130	13.6	55	5.8	29	3.0	2	0.2	20	2.0	346	36.4	954	100

in the early part of the study to 95 per cent in the last few years. The technique used in the examinations has been previously described and need not be repeated.^{1, 2} Histologic examination of the lungs was included as a part of every autopsy; in non-macerated fetuses and in all liveborn infants the liver, kidneys, thymus, and brain were also invariably included, and in the majority, the spleen, pancreas, suprarenals, thyroid, pituitary, and gonads were also studied histologically. The liver and suprarenal glands of all macerated fetuses were examined for the possible presence of the *Trepenoma pallidum*. Bacteriologic investigations were included when indicated, and during the past few years cultures of the lungs and the heart's blood have been a routine part of each autopsy. All placentas were subjected to gross and microscopic examination.

It was possible to find anatomic evidence of the probable cause of death in over 90 per cent of infants at term who died during labor or after birth (Table II). In association with all deaths the number of cases in which pathologic changes can be demonstrated decreases with decreasing length of gestation, and with earlier death in relation to delivery. When death occurred before the onset of labor and the fetuses had not yet arrived at the stage of viability, pathologic lesions were visible in only 24 per cent. In the entire series of 954 autopsies, demonstrable abnormalities were present in 64 per cent. (Maceration was not considered a pathologic change.)

Evidence of *anoxia* occurred more frequently than any other abnormal condition (Table III). It was most common when death occurred during labor and was found with almost equal frequency in premature and term infants. The diagnosis was based on the presence of discrete petechial hemorrhages in the lungs or thymus and/or petechial hemorrhages in the brain substance. The latter were often visible

TABLE II. NUMBER OF AUTOPSIES PERFORMED AND PERCENTAGE SHOWING PATHOLOGIC LESIONS ACCORDING TO TIME OF DEATH AND PERIOD OF GESTATION

PERIOD OF GESTATION	ANTE PARTUM		INTRA PARTUM		NEONATAL		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Previsible	71	24.0	23	34.8	78	39.8	172	32.6
Premature	125	43.2	70	74.3	218	70.7	413	63.0
Term	110	52.7	105	90.5	154	90.9	369	79.2
Total	306	42.2	198	78.3	450	72.0	954	63.8

only on microscopic examination. Marked generalized congestion of all viscera was almost always associated and interstitial or intra-alveolar pulmonary hemorrhages were occasionally found. There were 78 additional infants in whom no abnormalities could be demonstrated, plus 75 more who were unexamined at autopsy where clinical evidence seemed to indicate that death was due to anoxia. It was also present as a complicating factor in 44 infants with traumatic hemorrhage, 29 with malformations, 12 with pneumonia, and 6 with miscellaneous conditions. This makes a total of almost 40 per cent of all infants in whom anoxia was causative or contributory to death.

Traumatic hemorrhage was believed to be the cause of death only slightly more than one-half as often as was anoxia. Included were 114 cases of intracranial hemorrhage, one injury of the spinal cord, 2 severe suprarenal hemorrhages, and 4 infants with ruptured hematomas of the liver. The last 7 infants were all born alive; two were premature, 5 were at term. The intracranial hemorrhage was from the dural sinuses as a result of rupture of the tentorium in 32 infants, cerebral vessels with hemorrhage into the subdural space 16, choroid plexus with hemorrhage into one or more ventricles 11, vein of Galen 10, multiple sources 37, unstated 9. There were 9 additional fetuses who showed hemorrhage within the skull who died before the onset of labor. In those it was believed that the bleeding probably

The fetuses who died before the onset of labor present one of the most baffling problems related to infant mortality. They comprise almost one-third of the total fetal and infant deaths and in a large proportion the cause of death is entirely unknown. The existence of maceration makes autopsy examination somewhat more difficult but in general it does not destroy pathologic lesions which may have been present before the fetus died. In spite of detailed gross and histologic examination no abnormalities could be demonstrated in over one-half of the fetuses in this group (Table III). It is evident that except in those with malformations and erythroblastosis (and perhaps even in these two groups) the cause of death must be sought in the fetal environment.

In association with slightly over one-half of the deaths before the onset of labor, known environmental conditions were present which may well have contributed to the fatal outcome. The majority of these consisted of disturbances preventing normal exchange of metabolites between fetal and maternal circulation; they were present in 33 per cent, and include premature detachment of the placenta, 63; placenta previa, 16; cord prolapse and entanglement, 27; maternal shock, 3; and other miscellaneous conditions, 18. Maternal toxemia was present in 17 per cent. The way in which toxemia affects the fetus is in general unknown for in only a small number is infarction of the placenta advanced to a sufficient degree to be responsible. The same is true of medical complications of the mother. In neither of these groups is definite proof available that they are the actual cause of death, although the incidence of such maternal states is much higher among fetuses who died than among those who survive. There were six mothers whose Wassermanns were positive at some time during pregnancy but in none was syphilis demonstrable in the fetus.

Such things as premature rupture of membranes (41), hydramnios (11), abortion threatened during pregnancy (15), although indicating a disturbance in the intra-uterine environment can in no way be directly indicted as a cause of death. In death occurring before the onset of labor, the method of delivery can play no part in producing the fatality. Therefore in 40 per cent of the total ante-partum deaths the cause is entirely unknown, in 10 per cent the cause is present in the fetus, and in 50 per cent a possible cause is present in the mother.

Deaths Occurring During Labor or Delivery

Among the 242 fetuses who died during labor or delivery the proportion at term was considerably greater than among those dying in the ante-partum period or those dying after birth. Only 22 per cent of the total group failed to show pathologic lesions in contrast to 58 per cent among those who died in the ante-partum period. Evidence of anoxia was the most common condition found (Table III), with major malformations second, and intracranial hemorrhage third. Intrauterine pneumonia, erythroblastosis, and increased intracranial fluid were the only other conditions demonstrated. In this group the incidence of intracranial hemorrhage demonstrable at autopsy among infants at term is approximately three times that among premature infants and over four times that of previable infants.

The most common *maternal complications* were placenta previa and premature detachment of the placenta. These were associated with 26 per cent of all intra-partum deaths, and except in four instances where major malformations were present, interference with intrauterine oxygenation of fetal blood was presumably the cause of death. Prolapse or entanglement of the umbilical cord caused an additional 17 per cent of deaths from anoxia. Three of these fetuses were malformed.

Toxemia was present in 13 per cent of the mothers. Among these fetuses, 5 were not examined at autopsy, 8 showed no pathologic lesions, 9 showed petechial visceral hemorrhages, 7 intracranial hemorrhage, 3 were malformed, and 1 had erythroblastosis.

occurred after death. It was also found, but was considered secondary, in association with 5 deaths from anoxia, 7 from pneumonia, 3 from malformations, 2 from erythroblastosis, and 1 from syphilis. Mild edema of the meninges with some extravasation of blood into the cerebrospinal fluid is often found when death is due to anoxia. Such findings were not included as traumatic hemorrhage.

Major malformations were present in the same number of infants and fetuses as were fatal traumatic hemorrhages (14 per cent of the total autopsies). The incidence was slightly higher among infants at term than among those that were premature or previsible; death occurred more commonly during labor than before labor or after birth. The malformations included: involvement of the brain and spinal cord, 45; heart, 19; gastrointestinal tract, 8; kidney, 4; skeleton, 2; other, 7; multiple locations, 45. In ten additional infants, malformations were present but were not considered the cause of death. If the incidence of malformations is the same among the 20 per cent of infants and fetuses who were not examined at autopsy as among those who were, the incidence of malformations as a primary cause of death is one in every 170 births.

Pneumonia was found as the primary cause of death in 6 per cent of all fetuses and infants. The incidence was twice as great in infants at term as in those who were premature or previsible, and was twice as common among infants who died after birth as among those who were born dead. One premature infant who lived for twenty-one days had an associated septicemia and pyoarthritis. There were no deaths from primary gastrointestinal, cord, or skin infections. There were also 9 infants with pneumonia, and 4 with other infections in whom death was believed primarily due to intracranial hemorrhage, malformations, or anoxia.

Blood dyscrasias were the cause of death in 29 infants and fetuses. Three of these were diagnosed as *hemorrhagic disease* of the newborn; all were in infants at term who were born alive and who died more than forty-eight hours after delivery. It was believed to be the cause of death in one additional infant who was not examined at autopsy. This makes only 4 fatal cases of hemorrhagic disease among almost 28,000 babies, an incidence of one in 7,000. This is an interesting finding in relation to the recent recommendations that have been made concerning the administration of vitamin K to every pregnant woman prior to delivery. Although the reported incidence of fatal hemorrhagic disease in some institutions has been somewhat higher than ours, it still seems hardly feasible to give any medicinal preparation to several thousand women in order to possibly prevent one death; this is especially true when the drug can be given directly to the infant with immediate relief of symptoms when the diagnosis of an abnormal prothrombin time is made.

Erythroblastosis made up the other 26 cases of blood dyscrasias. The diagnosis was based on the presence of ectopic areas of erythropoiesis throughout the body, marked increase in the number of erythrocytes in the circulating blood, and an enlarged spleen. The incidence in this hospital is approximately 1:1,000 births.

The number of syphilitic infections is surprisingly small. There were only 6 infants in whom evidence of the disease could be found at autopsy. In only two of these was it believed to be the primary cause of death. One of the mothers was unregistered, had had no prenatal care, and was admitted to the hospital already in labor. There were 27 mothers with a history of a previous syphilitic infection or with a positive Wassermann test sometime during pregnancy, but whose infants gave no evidence of syphilis at autopsy.

Deaths Occurring Prior to the Onset of Labor

Among the 372 fetuses who died prior to the onset of labor almost half were macerated; while in the remainder who showed no definite evidence of maceration, labor must have been short and death must have occurred within a very short time before labor began.

TABLE IV. PROBABLE CAUSE OF DEATH IN 1,173 FETUSES AND INFANTS

CAUSE OF DEATH	ANTE-PARTUM DEATHS		INTRA-PARTUM DEATHS		NEONATAL DEATHS		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Anoxia	127	34.2	110	45.4	100	18.0	337	28.7
Placenta previa	16	4.3	21	8.7	34	6.2	71	6.0
Premature placental detachment	63	17.0	31	12.8	25	4.5	119	10.1
Cord prolapse or entanglement	27	7.3	35	14.4	15	2.7	77	6.6
Miscellaneous or no known cause	21	5.6	23	9.5	26	4.6	70	6.0
Birth trauma	0	0	33	13.7	119	21.3	152	13.0
Gross hemorrhage			30		91			
Clinical (no autopsy evidence)			3		28			
Major malformations	29	7.8	36	14.9	65	11.3	130	11.1
Infections, acute	5	1.3	6	2.5	44	7.9	55	4.7
Syphilis	0		0		2	0.4	2	0.2
Erythroblastosis	9	2.4	2	0.8	18	3.2	29	2.5
Miscellaneous	0		2	0.8	18	3.2	20	1.7
No pathologic lesions (or no autopsy)								
Premature	133	35.8	27	11.2	142	25.6	302	25.7
Toxemia	41	11.0	11	4.5	21	3.7	73	6.2
No abnormalities (non-toxic)	73	19.7	11	4.5	86	15.6	170	14.5
No autopsy (no pertinent maternal complications)	19	5.1	5	2.2	35	6.3	59	5.0
Term	69	18.5	26	10.7	51	9.1	146	12.4
Toxemia	21	5.6	11	4.5	19	3.4	51	4.3
No abnormalities (non-toxic)	32	8.6	4	1.7	10	1.7	46	3.9
No autopsy (no pertinent maternal complications)	16	4.3	11	4.5	22	4.0	49	4.2
	372	100.0	242	100.0	559	100.0	1,173	100.0

Other maternal conditions which constituted the only known abnormalities included: bleeding of unknown cause during pregnancy, 36; uterine inertia, 3; contracted pelvis, 23 (most of these were delivered by cesarean section); difficult delivery, 28; ruptured uterus, 3; and maternal shock of unknown cause, 2.

Premature rupture of the membranes occurred in 14 per cent of the patients in whom there were no other known complications. Twenty-three of these infants died as a result of intracranial hemorrhage, 11 of pneumonia, and 12 of anoxia. Twelve were grossly malformed, 19 showed no pathologic lesions, one had marked edema of the meninges, and 18 were not examined at autopsy. It is probable that some of these deaths were due to the increased difficulty in labor and delivery which may be attendant on the absence of amniotic fluid. The majority of infants with pneumonia died within a few hours of birth; the infection probably had its inception in utero as a result of the aspiration of infected amniotic material.

Twenty per cent of the deaths were unassociated with known complications of any kind. The infants of these women died of intracranial hemorrhage (9), anoxia (18), malformations (19), pneumonia (5), erythroblastosis (5), and edema of the meninges (2); twenty-one showed no abnormalities, and 19 were unexamined at autopsy.

Method of Delivery

The method of delivery of all infants born in the hospital is shown in Table V. The proportionate number of deaths and stillbirths in relation to the total number of

Difficulty in the passage of the fetus through the birth canal either from inadequate size of the bony pelvis or uterine inertia was present as the major complication in nine instances. The intracranial hemorrhage which was found in four of these fetuses probably resulted from the difficult delivery.

Syphilis had been diagnosed during pregnancy in the mothers of 3 fetuses; two showed intracranial hemorrhage and the third was malformed, but in none could syphilis be demonstrated.

Premature rupture of membranes (42), hydramnios (10), and abortion threatened during early pregnancy (8) were probably not related to death. The only other environmental conditions of any importance were 7 instances of severe maternal shock, due to premature detachment of the placenta (1), ruptured uterus (4), and unknown cause (2).

Deaths Occurring After Birth

Neonatal deaths numbered 559 and made up 48 per cent of the combined infant and fetal mortality. Although only 5.4 per cent of all the babies delivered alive in the hospital during the period of study were viable prematures, this group accounts for 48 per cent of the deaths. The previable infants make up an additional 16 per cent of the total mortality. The mortality rate for viable premature infants (weighing 1,000 to 2,500 Gm.) born alive in this institution is 19 per cent, and for term infants 0.7 per cent, the neonatal mortality for viable prematures thus being 27 times that of term infants. Seventy per cent of the 559 infants lived less than twenty-four hours.

Four hundred and fifty of the infants who were born alive were examined at autopsy. Over one-fourth showed no pathologic lesions, but of these 47 were previable, 64 were premature, and only 15 were at term. The most common abnormality was intracranial hemorrhage, with evidence of anoxia occurring almost as frequently. In the majority of these in the latter group, respiratory activity was never established. Malformations were third in importance, and pneumonia, although much less frequent than the other conditions, assumed a constantly increasing importance as a cause of death as the infant became older.

The *most common maternal complications* in this group are, like those in the still-born group, conditions leading to interference with intrauterine circulation. They were found in association with 20 per cent of the deaths which occurred after birth and include 49 cases of placenta previa, 37 of premature detachment of the placenta, and 26 of cord prolapse or entanglement. It is interesting to note that among the 95 women with placenta previa whose infants died in the ante-partum, intra-partum, or neonatal period there were only 4 with malformations, an incidence of about 4 per cent; among the 1,078 mothers who did not have placenta previa, the incidence of malformations was 11.8 per cent.

Maternal toxemia (including 6 cases of eclampsia) was present in association with 14 per cent of all deaths after birth. There does not seem to be any definite relationship between this condition and the anatomic lesions demonstrated at autopsy. Among the 74 infants in this group 13 had intracranial hemorrhage, 9 malformations, 7 evidence of anoxia, 5 erythroblastosis, 5 edema of the meninges, 4 pneumonia; 15 were not examined at autopsy, and 16 showed no pathologic lesions.

Various medical complications unrelated to pregnancy (exclusive of syphilis) were found as the only complications in 8 per cent of the cases. Fifteen were moderate or severe upper respiratory infections; the remainder were diabetes mellitus, cardiac conditions, hyperthyroidism, etc. There appeared to be no relation between these conditions and the causes of death. Syphilis as shown by a positive Wassermann test was found in nine mothers but in only one of these was syphilis proved in the infant.

Cesarean section shows the unexpectedly high mortality of 5.3 per cent. A greater proportion (67.0 per cent) of these infants were premature than were those delivered by any other method. The greatest single cause of death among these infants who were examined at autopsy was anoxia, with prematurity without pathologic lesions, second. Edema of the meninges is much more common following birth by cesarean section than it is in any other group.

The mortality associated with delivery by mid- or high forceps is almost four times that following low forceps. Two-thirds of these infants who were examined at autopsy gave evidence of intracranial hemorrhage, a greater incidence than was found in any other group. The incidence of prematurity (12.5 per cent) was lower than in any other group.

TABLE VI. PATHOLOGIC LESIONS DEMONSTRATED AT AUTOPSY IN INFANTS WHO MIGHT HAVE BEEN AFFECTED BY THE METHOD OF DELIVERY

	NUMBER CASES	TERM, NO ABNOR- MAL- ITIES	PREMA- TURE, NO ABNOR- MAL- ITIES	ANOXIA	TRAU- MATIC HEMOR- RHAGE	INFEC- TIONS	OTHER
Cephalic, spontaneous	141	7.2%	20.5%	39.9%	19.1%	10.6%	2.8%
Cephalic low forceps	53	9.4%	3.8%	32.0%	34.0%	17.0%	3.8%
Cephalic midforceps	33	6.1%	6.1%	12.0%	66.6%	8.0%	0.0%
Cephalic version and ex- traction	29	0.0%	6.9%	37.9%	48.3%	6.9%	0.0%
Breech	60	1.7%	23.3%	18.3%	43.4%	10.0%	3.3%
Cesarean section	61	8.2%	19.6%	36.3%	6.5%	13.1%	16.3%
	377	6.1%	16.2%	32.1%	29.4%	11.4%	4.8%

The high mortality following delivery by version and extraction deserves special comment. Except for the delivery of a second twin the procedure is rarely used in this hospital unless a maternal or a fetal indication for immediate delivery exists. This means that the life of the fetus is usually gravely threatened before the operation is performed. The mortality following version and extraction for the delivery of a second twin is only 4 per cent if 2 macerated fetuses are excluded; even then 3 of the 5 deaths which occurred were in infants under 2,000 Gm. and were probably due to prematurity rather than to the operative procedure. Among 12 infants weighing over 1,000 Gm. 35 per cent died during labor or after birth when the version was performed for other indications. In this 35 per cent (44 infants), a Voorhees bag was used to induce labor in 23 because of placenta previa, toxemia, or other complications. The most common indications for the version among the 21 who went into labor spontaneously were placenta previa or a prolapsed cord, but in all cases a serious complication was present. In very few instances could the method of delivery be indicted as productive of injury resulting in death.

Gravidity

The total number of women delivered include 12,615 primigravidas and 14,397 multigravidas. The incidence of deaths and stillbirths among multigravidous women is 5.2 per cent, a considerably higher rate than among the primigravidas (3.4 per cent). The incidence of intra-partum deaths is approximately the same in the two groups (primigravidas, 0.88 per cent; multigravidas 0.92 per cent), the incidence of neonatal deaths is slightly higher in women who have had previous pregnancies (2.43 per cent) than in those who have not (1.72 per cent), but the greatest difference lies in the ante-partum deaths where the rate is almost 1 per cent higher among multigravidas (1.80 per cent) than among primigravidas (0.89 per cent).

cases delivered by each method is lower following the use of low forceps than in any other method of delivery. This is largely because forceps are rarely applied to a macerated fetus or one which is previsible or malformed. In order to arrive at a conclusion concerning the importance of the method of delivery in relation to mortality, it is necessary to eliminate all fetuses dying before the onset of labor, all who are born before reaching viability, and all suffering from malformations, erythroblastosis, and syphilis. This eliminates the group in whom delivery could not have been related to the fatal outcome, and leaves only those whom delivery may have affected.

The figures thus obtained (Table V) show an identical rate for infants with the cephalic pole presenting who are delivered naturally and with the aid of low forceps. Forceps are less frequently applied to premature than to term infants, and the proportion of prematures who died following forceps delivery was only 27 per cent of those delivered by this method; whereas 63 per cent of the infants dying after natural delivery were premature. Knowing that the general prognosis for survival of

TABLE V. MORTALITY IN RELATION TO METHOD OF DELIVERY*

METHOD OF DELIVERY	I TOTAL HOSPITAL DELIVERIES	III TOTAL DEATHS		III DEATHS POS- SIBLY RELATED TO METHOD OF DELIVERY		IV PERCENTAGE OF PRE- MATURES IN COL. III
		NO. OF DEATHS	% OF TOTAL DELIV- ERIES	NO.	% OF TOTAL DELIV- ERIES	
Natural cephalic	16,440	498	3.1	191	1.1	63.3
Low forceps	6,832	100	1.5	74	1.1	27.0
Mid- or high forceps	1,133	59	5.2	48	4.3	12.5
Version and extraction	246	72	29.3	49	22.0	51.0
Breech	1,050	208	19.8	86	9.3	61.6
Cesarean section	1,462	127	8.7	76	5.3	67.1
Other	158	109	69.0	37	40.3	56.7
	27,321	1,173	4.3	561	2.0	52.3

*All infants dying in the ante-partum period, those delivered before the period of viability, and all suffering from malformations, erythroblastosis, and syphilis are eliminated.

premature infants is much poorer than that of term infants, one would expect a higher mortality in the naturally delivered group on the basis of the greater number of prematures. Since this is not found, it indicates that with equal percentages of prematures in both groups, the mortality would be proportionately higher after forceps delivery than after natural delivery. Of the infants who were examined at autopsy, the incidence of intracranial hemorrhage was almost twice as great among those delivered by low forceps as among those delivered naturally and makes the leading cause of death in the low forceps group (Table VI). There was a much smaller proportion (4 per cent) of infants delivered by forceps who were normal appearing prematures than among those delivered naturally (20 per cent). Evidence of anoxia was the principal lesion found in the natural cephalic deliveries.

Mortality following breech delivery after appropriate corrections are made is over 8 times that of natural cephalic delivery. The proportion of prematures to the total deaths in each group is almost identical so that the excessive numbers of prematures do not seem to be a factor. Intracranial hemorrhage was the principal pathologic lesion (43.4 per cent) in those examined at autopsy. This group has a higher incidence of prematures without pathologic lesions (23.3 per cent) than does any other.

TABLE IX. CAUSE OF DEATH IN RELATION TO DEATH RATE PER 1,000 BIRTHS IN EACH FIVE-YEAR PERIOD OF MATERNAL AGE

	15-19		20-24		25-29		30-34		35-39		40-44	
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
No abnormalities	25	12.0	56	6.5	96	12.0	82	15.0	50	22.0	17	31.0
Anoxia	9	4.2	58	6.7	73		49	9.1	36	16.0	11	20.0
Traumatic hemorrhage	6	2.8	39	4.5	32	4.0	34	6.2	11	4.9	5	9.2
Malformations	11	5.2	42	4.9	33	4.1	22	4.0	14	6.2	7	12.0
Infections, acute	3	1.4	10	1.5	21	2.6	8	1.5	10	4.4	4	7.4
Syphilis	0		2		0							
Erythroblastosis	1	0.5	4	0.4	12	1.5	6	1.1	4	2.0	1	1.6
Miscellaneous	0		3	3.4	9	1.1	5	0.9	1	0.4	2	3.6
Total	55	26	214	28	276	25	211	38	126	56	47	85
Total deliveries	2106		8640		7992		5508		2241		540	

same age period. This would suggest that until after 40, advancing age does not increase the probability of malformations. Increasing age in general, however, carries a proportionately greater probability of an unsuccessful outcome to pregnancy.

Sex

In the total number of stillborn fetuses, 52.2 per cent were males, 47.8 per cent females; the ratio was identical in deaths occurring in the ante-partum and intra-partum periods. A greater proportion of males (59.2 per cent) to females (40.8 per cent) was found in the infants dying after birth. The preponderance of males over females is slight among the infants and fetuses dying in the previable period (51.0 per cent males) and rises in the premature group (55.2 per cent males) to reach its height among the infants at term (59.7 per cent males).

The ratio for the country as a whole averages 51.2 per cent males among all reportable live births; that for an eight-year period at the Chicago Lying-in Hospital is 52.9 per cent males. In the present series, the ratio among all stillborn fetuses and among all fetuses and infants dying in the previable period was approximately equal to that in the general birth rate. Among infants who were born alive and subsequently died, and among all of those, both liveborn and stillborn who were at term before death occurred, the ratio of males was abnormally high. This is in contrast to a frequently found statement that the earlier death occurs during the course of pregnancy the higher the proportion of males.

In the total 1,173 fetuses and infants, 55.5 per cent were males, 44.5 per cent females. The causes of death in the two groups failed to show notable variations. The highest percentage of males, falls in the groups with evidence of trauma (60.87 per cent), the lowest in the group of malformations (45.8 per cent) (Table X).

TABLE X. CAUSE OF DEATH IN RELATION TO SEX

	MALE %	FEMALE %	TOTAL NUMBER
Anoxia	57.3	42.7	242
Traumatic hemorrhage	60.8	39.2	130
Malformations	45.8	54.2	130
Infections, acute	56.6	43.4	55
Syphilis	100.0	0	2
Erythroblastosis	46.4	53.6	29
Miscellaneous	55.0	45.0	20
No abnormalities	54.3	45.7	346
No autopsy	57.3	42.7	219
Total	52.5	47.8	1173

When divided according to length of gestation, the infants of the multigravidas show a somewhat higher death rate in all groups, the greatest difference being found among the prematures; the incidence of deaths and stillbirths during the premature period is 1.3 per cent for primigravidas 2.3 per cent for multigravidas. Multigravidas show proportionately many more ante-partum deaths at term (105) than do primigravidas (38).

Among the 927 infants and fetuses who were examined at autopsy, the only two causes of death which were proportionately higher among primigravidas were birth trauma and malformations (Table VII). All of the causes of hemorrhagic disease occurred in babies of primigravidas; all erythroblastosis occurred in those of multigravidas.

TABLE VII. MATERNAL GRAVIDITY IN RELATION TO CAUSE OF DEATH AS DEMONSTRATED BY 954 AUTOPSIES

	PRIMIGRAVIDAS	MULTIGRAVIDAS	TOTAL
	%	%	%
Anoxia	22.4	27.5	25.4
Traumatic hemorrhage	20.0	10.0	13.6
Malformations	17.9	12.0	13.6
Infections, acute	5.9	6.1	5.8
Syphilis	0	0.3	0.2
Blood dyscrasias	0.9	4.2	3.0
Miscellaneous	0.9	2.9	2.0
No abnormalities	32.0	37.0	36.4
Total	100.0	100.0	100.0

Maternal Age

Both stillbirths and neonatal deaths rise constantly in number in direct relation to advancing maternal age. Sampling the age distribution of 2,000 mothers and basing the calculations on a similar expected distribution in the entire group the combined rate rises from 3.2 per thousand deliveries in the age groups of 15 to 19 and 20 to 24 to 10.8 between the ages of 40 and 44 (Table VIII). Beyond 24 years of age there is a constant, steady rise in the ante-partum, intra-partum and neonatal deaths. There is a striking rise in the ante-partum and intra-partum deaths between ages 40 and 44. The neonatal deaths, however, are slightly less than in the preceding age group.

TABLE VIII. FETAL AND INFANT MORTALITY IN RELATION TO MATERNAL AGE

MATERNAL AGE	DISTRIBUTION OF TOTAL BIRTHS	DISTRIBUTION OF TOTAL DEATHS	DEATH RATE PER 1000 BIRTHS			
			AP	IP	MND	TOTAL
15-19	7.8%	5.7%	0.8	0.6	1.8	3.2
20-24	32.0%	23.7%	0.7	0.8	1.7	3.2
25-29	29.6%	29.3%	1.5	0.8	1.9	4.3
30-34	20.4%	22.1%	1.6	0.9	2.2	4.7
35-39	8.3%	14.0%	2.7	1.1	3.6	7.4
40-44	2.0%	5.2%	5.3	2.4	3.1	10.8
Total	100.0%	100.0%	1.3	0.8	2.0	4.3

When the rates are investigated in relation to cause of death a general increase is found in practically all causes as maternal age advances (Table IX). It is interesting to note that the incidence of malformations remains practically the same up to 40 years of age; the rate for 40 to 44 is practically double that of the preceding groups, but the increase is proportionately less than it is for any other cause in this

when the acute symptoms had subsided, but with continued treatment in the clinic, the residual exudate decreased markedly in size or was completely absorbed.

With a history of repeated attacks, removal of a single tube and ovary is no surety that the patient will not have trouble subsequently on the other side. Six of our patients had a unilateral salpingo-oophorectomy before presenting themselves to us. In several instances of repeated re-infections, we have performed bilateral cornual resection of the tubes with satisfactory results.²

Most of the patients coming to operation were asymptomatic, and they were persuaded with difficulty to be re-admitted to the hospital. The symptoms, if any, and the size of the mass were our only criteria for advising operations. At these operations, no pus tubes or strictly ovarian abscesses were found. Pus, when encountered, was encapsulated in a thick fibrous wall involving both tube and ovary, a true tubo-ovarian abscess. The pus was sterile on culture. All operated patients had uncomplicated postoperative courses.

Summary and Conclusions

1. Results are reported in the treatment of 94 cases of acute pelvic inflammatory masses of tubal origin, by acetyl beta methyl choline chloride iontophoresis.

2. Absorption of the adnexal mass and exudate was apparently complete in 80 per cent of the cases.

3. Eighty-nine per cent of the patients were asymptomatic and able to perform all their usual duties within eighteen weeks.

4. Each patient's follow-up was terminated by tubal insufflation test, operation, or by pregnancy.

5. Of 75 patients who were asymptomatic and who had complete absorption of their pelvic mass, 60 (80 per cent) had nonpatent tubes, 15 (20 per cent) had patent tubes determined by insufflation or verified by pregnancy; 8 patients became pregnant.

6. If given adequate treatment, acute inflammatory pelvic exudates will be absorbed by acetyl beta methyl choline chloride iontophoresis except where a fibrous thick-walled localized tuboovarian abscess forms.

7. We believe that acetyl beta methyl choline chloride iontophoresis is a valuable adjunct in the treatment of acute pelvic inflammation of tubal origin.

References

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104 EAST SEVENTY-FOURTH STREET.
60 SEAMAN AVENUE

Summary

A summary of the probable causes of all stillbirths and infant deaths at the Chicago Lying-in Hospital for a ten-year period is found in Table III. Interference with the circulation of the fetus while it is still in utero appears to cause more deaths than any other condition. With death occurring before the onset of labor this is most commonly premature placental detachment; with death during labor it is most often cord prolapse or entanglement; and in death after birth it is most often placenta previa. In actual numbers premature placental detachment occurred with one and one-half times the frequency of the other conditions.

Second in importance is prematurity, although it is highly probable that this should rank first because the combination of a harmful maternal complication and prematurity is doubtless more likely to result in a fatality after birth than would be the same complication acting on an infant at term. The fetuses who die before the onset of labor and the majority of those dying during labor cannot be considered to have died because of prematurity. The total number of prematures who die without specific lesions and whose deaths are probably due to inadequate development make up 25.6 per cent of deaths after birth, but only about 12 per cent of the total mortality.

Birth trauma accounts for 13 per cent of the deaths. Included with the infants showing specific intraeranian hemorrhage are 31 infants who either were not subjected to autopsy or who exhibited no gross bleeding, but in whom there was difficulty in effecting delivery or in whom there was clinical evidence of trauma in the infant after birth.

Major malformations are almost equal to trauma as a cause of death. In deaths occurring in the neonatal period, malformations are second only to prematurity as a causative factor.

Infections are not common during this period, and the few which are found consist almost entirely of pneumonia.

Erythroblastosis, syphilis, and a few miscellaneous conditions make up the remainder of the conditions producing death.

Conclusions

Stillbirths and deaths among infants during the first ten days of life are almost entirely due to conditions affecting the fetus before or during birth and are only rarely due to diseases which are intrinsic in the fetus or which result from exposure to deleterious influences after birth. Seventy per cent of all the infants who were born alive but who ultimately died before leaving the hospital survived less than twenty-four hours.

The most common lesions demonstrable at autopsy were those indicative of anoxia; traumatic hemorrhage and malformations tied for second place.

Spontaneous cephalic delivery and delivery by low forceps were associated with the same proportionate number of deaths. A proportionately greater number of deaths followed all other methods of delivery.

The total death rate was higher among multigravidas than primigravidas and constantly increased with advancing age.

References

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Editorial

Artificial Insemination

THE control of fertility on the one hand and the relief of sterility on the other are among long-standing questions which have occupied the attention both of the medical profession and the laity. The attempts to solve the problems associated with them have developed methods and procedures not always associated with sincere beliefs and honesty. Propaganda, often hysterical and far from altruistic, has been combined with commercialism to a degree which has interfered with, rather than furthered, scientific progress. The lay mind frequently is inflamed in its demands upon professional sources for relief from sterility for example, and the opportunity has not been neglected by those who have found it a source of profit and aggrandizement. And, in attempting to stem the tide, the seeker for truth finds his way impeded by accusations of narrow mindedness and lack of vision, if nothing more.

A phase of this subject which has been given widespread attention in recent years is the relief of childlessness sterility in the wife by resort to artificial insemination from a donor not the husband of the patient. The procedure designated as homologous insemination may be justified and is not here under consideration. On the other hand, the legal, ethical, and religious considerations involved in the heterologous variety have become subordinated in the attempt to satisfy a woman desirous of bearing her own child. It would appear that the transfer of the experiences of veterinary practice to the human subject have been employed without a full recognition of the civilized acceptance of the marriage state as a prerequisite to the legitimacy of offspring. This somewhat broad construction may be objected to by those who believe, and perhaps quite honestly, that, in exceptional cases, a resort to such practices is justified. The increasing knowledge about the physiology of human reproduction, however, must lead to the inevitable conclusion that the need for heterologous artificial insemination is steadily diminishing. The publicity which has been given to the procedure through certain glamorous articles in the medical and lay press, moreover, can only be regarded as unfortunate and misleading.

The claimed results by certain proponents of the popularly designated "test-tube baby" method must be subjected to critical analysis such as is attempted by Dr. Folsome in an article which appears in the current issue of the JOURNAL. Without access to personal histories and data, it could be based merely on the published paper, nevertheless it calls for careful reading. Among other things it is of interest to observe in Sey-

mour and Koerner's article* that in approximately 9,500 children "sired," as the authors term it, by this method, there were no malformations, a less than usual incidence of abortions and ectopics and, strangely, there is no mention of the usual proportion of twins. As Folsome succinctly states, normal coitus appears less successful than the suggested substitute.

Whether ethical considerations should be subordinated to those of a material character in an attempt to relieve sterility in a woman under the circumstances quoted, is more than an academic problem. Possibly scientific attainment can achieve certain successes in the human subject as it has in animals. But is it desirable to lower accepted human relationships in this respect and, in a sense, to place them on a level with the propagation of animal life undertaken for convenience and gain. If we are to set aside the fundamentals of marriage in carrying out this procedure, what would be the ultimate effects on our much vaunted modern civilization? The Christian and legal concepts of marriage, together with its rites and responsibilities, in the course of time, would likely be thrown into the discard. Can we afford to overturn at this or any other time the morality of the marriage state and approve the accompanying unphysiologic practices essential to carrying out the procedures advocated to overcome sterility in a group of frustrated women?

The problem referred to cannot be dismissed by a shrug of the shoulder. Its implications are much too serious. It is to be hoped that further discussion may be stimulated by Dr. Folsome's contribution.

Correspondence

The Richardson Composite Operation for Uterine Prolapse a Misnomer

To the Editor:

In the January, 1943, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there appeared an article by Drs. Richard W. Te Linde and Edward H. Richardson, Jr., entitled "End Results of the Richardson Composite Operation for Uterine Prolapse." The technique of this operation was devised and published by me in November, 1937 (AM. J. OBST. & GYNEC. 34: 814, 1937), under the title "An Efficient Composite Operation for Uterine Prolapse and Associated Pathology." In this paper there is included the following paragraph: "Now all of these requirements can be adequately met by judicious selection from such well-established vaginal operations as those discussed above, which are widely employed today in the treatment of vaginal hernias, certain of their most dependable features and combining these into a composite reconstructive plan more comprehensive in scope and of greater flexibility and efficiency than any one of the contributing models. In the operation about to be described this is precisely what I have done; consequently, no claim of originality is made in its presentation beyond that involved in the construction of what I believe to be an improved plan out of borrowed units for each one of which I hereby make grateful acknowledgment to the distinguished gynecologists who originally devised them." A reading of the context will reveal to anyone interested exactly why and how I happened to devise and recommend this operation. I wish now to state that this was done independently and that neither at the time of my publication nor since, until yesterday, March 23, 1943, had I the slightest knowledge that anyone else had preceded me in such an effort. On yesterday, however, thanks to the courtesy of Dr. Ludwig Emge, I received a reprint of an article which was published in 1919 by the late Dr. Alfred B. Spalding who, as many will recall, was Dr. Emge's predecessor at Stanford University School of Medicine, entitled "A Study of Frozen Sections of the Pelvis with Description of an Operation for Pelvic Prolapse" (Surg., Gynec. & Obst. 29: 529, 1919), in which he describes and illustrates a plan differing from my own only in minor details. And I may add that neither Dr. Te Linde nor my son, whose recent joint report is referred to above, knew anything about Dr. Spalding's prior publication.

I am happy, therefore, promptly and without reservation of any kind to concede full priority in the development and recommendation of this operation to the late Dr. Alfred B. Spalding. Furthermore, I feel sure that I can depend upon the assistance of my professional colleagues throughout the country, which I hereby earnestly solicit, in helping me identify this operation in all future publications as the "Spalding Operation for Uterine Prolapse."

EDWARD H. RICHARDSON, M.D.

Baltimore, Md.
March 24, 1943.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 13, 1942

The following paper was presented:

Genetic Effects of Radiation of the Germ Plasm. Ramsay Spillman, M.D. (by invitation).

MEETING OF NOVEMBER 10, 1942

The following papers were presented:

Carcinoma and Sarcoma in the Same Uterus. Benjamin P. Watson, M.D. (For original article, see page 1025.)

Breech Presentation Treated by Cephalic Version in the Consecutive Delivery of 1,700 Women. George H. Ryder, M.D. (For original article, see page 1004.)

MEETING OF DECEMBER 8, 1942

Moving Picture Demonstration of a Rapid Pregnancy Test. Dr. Samuel H. Geist.

The following papers were presented:

Reconstruction of the Human Oviducts. Results Obtained by a New Technique.

Dr. J. Randolph Gepfert. (For original article, see page 1031.)

The Status of Artificial Insemination. A Critical Review. Dr. Clair E. Folsome (by invitation). (For original article, see page 915.)

Department of Reviews and Abstracts

Selected Abstracts

Newborn

Richdorf, L. F., and Kearney, Wm.: Prothrombin Deficiency in the Newborn as Affected by Vitamin K and by Prelacteal Feeding, *Journal-Lancet* 62: 155, 1942.

The authors found that newborn infants have variable degrees of prothrombin deficiency. This deficiency manifests itself on the second, third, and fourth days of life. The deficiency was increased by starvation (feeding water only to the infant for 48 hours) which would indicate a possibility of a food disturbance as an etiologic factor in hemorrhagic disease. The use of prelacteal feedings had a favorable effect on the prothrombin deficiency. Infants that received one milligram of synthetic Vitamin K preparation intramuscularly maintained normal prothrombin times throughout the first six days of life.

WILLIAM BERMAN.

Davalos, Ricardo Callejas: Study of Psychoneurophysiologic Perceptions of Fetus and Newly Born, *Rev. méd. cubana* 53: 201, 1942.

Davalos states that at birth the middle ear and eustachian tubes are filled with a viscous, thick fluid and that the child is deaf until this viscous mold has disappeared. Partial hearing occurs by transmission of sound through the cranial bones. Taste can be demonstrated in premature children, and smell in anencephalic children from the beginning. At birth, the child has only two cutaneous feelings: agreeable and disagreeable. All cutaneous feelings are necessarily disagreeable at the beginning of extrauterine life, and the child reacts to them by squirming and crying. As the paths of nervous conduction develop, the general primary sensations gradually change into perceptions. Perception is present as soon as the child is capable of recognizing an object; at this time, the child acquires a perceptive interest in the object, and the perception is always associated with movement.

The perceptive interests develop during the first six months of life and are then replaced by motor interests. The child probably has visual sensations from birth on, but they are generally (light and darkness). Soon it shows signs of visual attention and its eyes follow brilliant objects. From two months on, its interest in what it sees increases gradually: red objects especially attract its attention, and it recognizes a number of familiar things.

The child distinguishes between familiar noises from two weeks on, but it reacts to the voice only after two or three months. At the end of the fourth month, it connects definitely sound with movement and, at six months, it perceives a whole range of modulations of various intensities, which have no verbal but a great intellectual significance. At this age, the child reacts vividly to music and especially its rhythm. At ten months, a wide range of sounds is exactly understood and, at twelve months, the entire cycle of pure sonority independently of words.

Tactile sensation in the newborn is extremely poor. When it is well developed, it becomes so to say displaced with the appearance of motility, the tactile sensitivity changing into usable motor sensitivity.

J. P. GREENHILL.

De Snoo, K.: Cause and Treatment of Icterus Gravis Neonatorum, *Monatschr. f. Geburtsh. u. Gynäk.* 113: 150, 1942.

There is a close connection between icterus gravis neonatorum, hydrops fetalis, habitual intrauterine death, and congenital anemia. The author believes that these are all different forms of the same disease which is familial in character. In all the cases, the placental villi are enlarged, irregular, occasionally edematous and show more or less centers of blood cell formation. The metabolic products of the stroma of the villi cause morbid symptoms in the infant. The treatment during pregnancy consists essentially of a salt-free diet. Premature labor should be induced. After delivery the baby should be given 30,000 I.U. of estrogen three times a day and 0.5 of vitamin K. Labor is induced primarily to prevent intrauterine death of the child. The estrogen is given to check blood destruction and the vitamin K to prevent hemorrhage.

J. P. GREENHILL.

Thompson, Samuel A., and Birnbaum, George L.: The Phenomenon of Asphyxial Resuscitation, *Surg. Gynec. & Obst.* 74: 1078, 1942.

Advanced asphyxia produced in dogs by tracheal obstruction can be relieved by suck and blow resuscitation using an inert gas. The percentage of dogs resuscitated in this manner is reported to exceed those which can be revived with manual artificial respiration, rhythmic inflation, or suction.

L. M. HELLMAN.

Birnbaum, George L., and Thompson, Samuel A.: The Mechanism of Asphyxial Resuscitation, *Surg., Gynec. & Obst.* 75: 79, 1942.

The authors have previously shown that in advanced asphyxia in dogs resuscitation could be effected by rhythmic inflation and suction with an inert gas. The present paper deals with the mechanism of this reflex, and also with various factors which tend to modify it. Again using dogs it was demonstrated that the addition of 10 per cent carbon dioxide, or bilateral vagus section, inhibited resuscitation. Denervation of the carotid seems either to have inhibited resuscitation, or greatly modified it, depending on the nature of the inert gas used. Resuscitation with inert gas by the suck and blow method was effective in 85 per cent of the experiments, while manual artificial respiration or rhythmic pressure alone, with nitrogen, effected resuscitation in only 12 to 20 per cent. Clinically the authors feel this should be of value.

L. M. HELLMAN.

Taricco, Giovanni: Contribution to the Etiology of Neonatal Tetanus, *Ginecologia* 16 (Series 2): 682, 1939.

The author reports a case of tetanus in the newborn. The portal of entrance was the umbilical cord. Symptoms appeared eight days following delivery. The infant died ten days later.

The pathology, differential diagnosis, treatment, and prognosis of tetanus in the newborn are discussed in detail. The author emphasizes three primary points to consider in the prophylaxis of tetanus in the newborn: (1) rigorous asepsis in the care of the umbilical cord; (2) passive immunization of the newborn with antitoxic serum; and (3) active immunization of the fetus can be secured, to some degree, via the placental passage of the antitoxins.

CLAIR E. FOLSOME.

Volpitto, P. P., and Torpin, R.: Apnoea Neonatorum: Its Treatment by a Simplified Insufflation Technic, South. M. J. 35: 559, 1942.

Factors of prime significance in the causation of apnoea are, anesthesia, anoxemia, analgesia, acapnia, prematurity, and trauma. Unrelieved apnoea leads to asphyxia with consequent irreversible nerve cell damage. The principles underlying the treatment of apnoea are, (1) Creation of a patent airway by removal of foreign material in the oropharynx and trachea; (2) adequate and immediate artificial respiration; and (3) maintenance of body temperature.

The two generally accepted methods of resuscitation include: (1) Those which employ extrapulmonic pressure principles (Drinker and Emerson respirators); and (2) Those using intrapulmonic pressure (mouth-to-mouth respiration; Henderson, Flagg, E & J Kreiselman resuscitators). The former are not suitable for infants. In the method recommended by the authors, a combination of mouth-to-mouth and Meltzer-Flagg principles is used. Their apparatus includes a laryngoscope with an infant blade, a rubber syringe for oropharyngeal suction, a No. 12 French woven-silk catheter, and a Torpin insufflator. The latter is of simple construction and consists of a circular metal trap with a weighted lid "pop-valve" which limits pressure to 20 cm., of water, and two tubes projecting from either side of the trap; one of these is for the catheter, and the other, for suction and insufflation. Advantages of the apparatus are simplicity, compactness, and low cost.

The infant is wrapped in a warm blanket and placed on a table with the head hyper-extended. Pharyngeal suction is carried out, and, then with the aid of the laryngoscope, the catheter is gently passed about an inch beyond the cords. After tracheal aspiration, insufflation may be performed, either by mouth-to-tube, or, by direct connection to an oxygen tank. With the latter, a simple finger adapter may be used to interrupt the flow of oxygen at any desired rate.

ARNOLD GOLDBERGER.

Uterine and Tubal Insufflation

Mocquot, P., Palmer, R., and Pulsford, J.: Importance of Some Technical Details in Hysterosalpingography, Rev. franç. de gynéc. et d'obst. 36: 1, 1941.

The authors recommend the use of a 20 per cent solution of lipiodol for hysterosalpingography because of its fluidity and diminished opacity in order to avoid confusing shadows. They recommend that the injection be discontinued very slowly in order to avoid contractions of the uterus. Manometric studies give valuable information about the physiology of the uterus and the tubes. In order to obtain the best results, particularly in salpingography, x-ray pictures should be taken with the patient in various positions.

J. P. GREENHILL.

Palmer, R., and Piguet, M.: Hystero-graphy With 20 Per Cent Lipiodol in Cases of Fibroids, Rev. franç. de gynéc. et d'obst. 36: 84, 1941.

The authors report a series of 13 cases of fibroids of the uterus in which hystero-graphy played an important role in the diagnosis and treatment. The authors consider the use of lipiodol a most important adjunct in the diagnosis of all intra-uterine conditions.

J. P. GREENHILL.

Hukata, Y.: Experimental Studies of Hysterosalpingography, Jap. J. Obst. & Gynec. 24: 24, 1941.

It was previously shown that ligation of the Fallopian tubes produces edema of the tubes. Ligation of the uterus likewise produces localized edema. The amount

of edema in the two Fallopian tubes after iodized oil was injected into only one tube was found to be greater on the injected side. The author concludes, therefore, that iodized oil stimulates edema. He further contends that when iodized oil escapes from the Fallopian tubes it produces adhesions in near-by structures.

The author also found that the sedimentation rate was increased after the use of hysterosalpingography. This is due to physiochemical stimulation by the iodized oil.

J. P. GREENHILL.

Breitlander and Hinrichs: Pulmonary Emboli After Hysterography Using Jodipin, Zentralbl. f. Gynäk. 65: 124, 1941.

A case is reported (Schwerin) in which hysterography had been performed in the presence of a tumor which subsequently proved to be a carcinoma. Immediately following the injection, the iodized oil preparation escaped into the uterine venous system and produced outspoken pulmonary embolism. No symptoms at all followed this course. A roentgenogram taken eighteen hours after the occurrence showed a wide distribution of the material in the lungs, particularly the right one. This observation confirms in human beings the experiments performed by Boelme in cats, that the movement of the venous blood stream is systolic and is dependent upon contractions of the left ventricle.

J. P. GREENHILL.

Stampfel, K.: Extensive Filling of Uterine Veins With Iodized Oil During Hysterosalpingography, Roentgenpraxis 13: 148, 1941.

Stampfel (Mabrisch-Ostrou) reports two cases of extensive infiltration of iodized oil into the uterine veins during intrauterine injection of iodized oil. It was striking that no discomfort at the time of injection or afterward was experienced. There was no sign of embolus. The author emphasizes that iodized oil should never be injected into the uterus without being followed by x-ray pictures. Furthermore, x-ray pictures should be taken twenty-four hours or more after the injection of the iodized oil.

J. P. GREENHILL.

Gerin-Lajoie, L.: Utero-Salpingography, Canad. M. A. J. 44: 555, 1941.

The author summarizes his technique for lipiodol injection of the uterus and tubes using observed pressures of not more than 35 mm. of mercury for the injection. He lists acute inflammatory conditions, pregnancy, and hemorrhage as contraindications. He believes that uterosalpingography is very useful in the study of patients with sterility, congenital malformations, tumors, and in the investigation of certain cases of uterine bleeding.

CARL P. HUBER.

Pineda, Rafael: Kymographie Insufflation in Sterility of Women, Bol. Soc. de obst. y ginec. de Buenos Aires 20: 849, 1941.

Pineda describes Rubin's kymograph and the technique of its use; he discusses its indications and contraindications and the dangers resulting from the faulty application and the wrong choice of the time for the test. These risks are easily eliminated by careful clinical and gynecologic examination. He mentions the sources of error and presents a series of tracings of normal tubal permeability, showing the type of oscillations, their form and amplitude. He refers to the clinical signs of permeability and particularly to pain in the shoulder after positive insufflation. Then he describes the tracings of tubal impermeability and spasm,

and of partial obstruction with intra- or extratubal lesion. He discusses the kymographic curves obtained in various patients, depending on their hormonal condition and sexual life and the results of kymographic therapy in sterility of woman.

J. P. GREENHILL.

Anesthesia, Analgesia, etc.

Samuel, M.: The Use of Evipan Sodium or Narconumal for Intravenous Anesthesia in Surgery, Gynecology and Obstetrics, *Monatschr. f. Geburtsh. u. Gynäk.* 112: 290, 1941.

More than 100 minor and major operations of a surgical, gynecologic, and obstetric nature were performed under intravenous anesthesia by Samuel. No adverse effect was observed on the fetus. Anesthesia was complete and no accidents were observed. The amount of anesthesia necessary was judged by the patients' response to questions during injections and to the presence or absence of reflex movements.

J. P. GREENHILL.

Whitehouse, Beckwith: Fragarine: An Inhibitor of Uterine Action, *Brit. M. J.* 2: 370, 1941.

In certain areas of England it is common practice for women to drink an infusion of dried raspberry leaves to allay the pains of labor, as well as to relieve dysmenorrhea. The author has directed a study of the pharmacologic action of raspberry tea, and presents a preliminary report.

An active principle, named "fragarine," was isolated, which was found to cause a momentary fall followed by a conspicuous rise in blood pressure in the non-pregnant, spinal cat. Simultaneously, relaxation of the uterus occurred. Like nicotine, the mechanism of action is apparently two-fold: the adrenal glands are stimulated to liberate epinephrine; and, the sympathetic ganglia are stimulated with the resultant discharge of inhibitory impulses down the hypogastric nerves.

On the isolated cat's uterus in vitro, fairly prolonged contractions occurred.

Uterine contractions were then measured in three puerperal patients by the intrauterine bag method. In each case, following the administration of fragarine, contractions diminished in force and frequency, secondary contractions were eliminated, and such contractions as occurred were evenly spaced. A slight fall in blood pressure was noted, without a subsequent rise. No toxic symptoms occurred. The action of pituitrin on the human uterus was inhibited by fragarine.

The author feels that while further work remains to be done, fragarine may have a useful clinical application in inhibiting uterine contractions.

It is of interest that following the publication of this article, the editor received several letters from English practitioners (page 528), all testifying to the efficacy of raspberry-leaf tea in shortening labor and allaying pains.

FRED L. ADAIR, AND RAYMOND L. YOUNG.

Philpott, N. W.: Local Anesthesia in Obstetrics, *Canad. M. A. J.* 45: 539, 1941.

Local anesthesia has a definite place in obstetrics. The chief indications are: (a) In toxic cases especially where the baby is premature; (b) if a general anesthetic is contraindicated or if a competent anesthetist is not available; (c) to aid in the spontaneous expulsion of the breech; (d) in any cesarean section if the patient is suitable, but especially in those cases complicated by placenta previa, severe cardiac disease, or by chronic nephritis.

THE "LATZKO" EXTRAPERITONEAL CESAREAN SECTION*

A Report Based on a Study of Twenty-Five Cases

HERVEY C. WILLIAMSON, M.D., AND MYRON E. GOLDBLATT, M.D.
NEW YORK, N. Y.

(From the Obstetric Service of the French Hospital)

DURING the past two decades the incidence of cesarean section has increased greatly. At the same time the indications for a transperitoneal approach have been pushed beyond the limits of safety in potentially infected cases, the result being that studies of any group of cesarean sections will almost invariably show infection, particularly peritonitis, to be the primary cause of death following this operation. Any experience with a procedure which will help reduce, if not entirely eliminate, this cause of death, namely by employing an extraperitoneal approach, should be of value.

History gives to Philip Syng Physick, professor of surgery at the University of Pennsylvania, the credit for the idea of separating the fundus of the bladder from the peritoneum as an approach to the lower uterine segment. This reference apparently passed unnoticed until Frank, of Cologne, made use of the idea in 1907. He pointed out that if the bladder was high it was possible to strip the peritoneum from the vault of this viscus. Frank, though successful in an occasional case, met great difficulty in separating the peritoneal fold from the bladder dome. These same difficulties were encountered by Sellheim (1908) in his numerous efforts to find a true extraperitoneal approach. The principle was almost abandoned when Latzko introduced his method of extraperitonization by lateral displacement of the bladder and upward and lateral displacement of the peritoneal reflection (1909). To Jellinghaus of New York belongs the credit of introducing and of popularizing the latter operation in the United States.

Many modifications of the so-called Latzko operation have been proposed, including those of Ricci, Smith, Frost, Waters, but what we wish to emphasize in this paper is that the operation which we do is the original Latzko type and that, as we do it, the operation is safe, simple, and does not require any more surgical skill than that which should be possessed by any one doing gynecologic surgery. It is not too time consuming. We have had some difficulty with the delivery of the head and have had to use forceps or the posterior blade of the Barton forceps in all the vertex cases. Many of the babies were quite large, the cause of the dystocia which necessitated the operation.

We have two basic ideas in presenting our experience with this operation: (1) to demonstrate the simplicity of the operation; (2) to stress

*Presented at a meeting of the New York Obstetrical Society, May 12, 1942.

Necrology

NORMAN R. KRETSCHMAR, Associate Professor of Obstetrics and Gynecology at the University of Michigan, died at Ann Arbor, on May 5, 1943, at the age of 39.

Item

Applications for the 1944 examinations of the Board are being received at the office of the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pennsylvania. Booklets of information regarding Board requirements and examinations, together with application forms, will be sent upon request.

All applications for the year 1944 must be in the Secretary's Office not later than November 15, 1943, ninety days in advance of the Part I examination date.

Candidates are required to take both the Part I and Part II examinations. The Part I examination consists of the written paper and the submission of twenty-five case history abstracts, and will be conducted on Saturday, February 12, 1944. This examination will be arranged so that the candidate may take it at or near his place of residence. Upon the successful completion of the Part I examination, candidates are eligible for the Part II examination consisting of a pathology and an oral examination. This is given at the annual meeting of the Board once each year, the time and place of which will be announced later.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations be encouraged to apply and that they request orders to "detached duty" for the purpose of taking the examinations whenever possible.

One per cent novocain with adrenalin minims 5 to every 150 c.c. is recommended. In 83 cesarean sections under anesthesia only 4 of the 80 babies born alive needed any active form of resuscitation. This is in direct contrast to the 83 babies delivered by cesarean section under general anesthesia where 23 babies had one or more active forms of resuscitation. The advantages for the mother are also many and include decreased blood loss, fewer pulmonary complications, and freedom from postoperative vomiting, distention, and ileus.

CARL P. HUBER.

Thomas, Herbert, and Taylor, Hoyt C.: *Anesthesia and Analgesia in Obstetrics (With a Report of the Use of Evipal Soluble)*, Connecticut M. J. 6: 327, 1942.

One hundred and ten unselected patients were given rectal evipal during labor. Of these, 66 primigravidas and 28 multigravidas were given evipal, and scopolamine; 9 primigravidas and 7 multigravidas were given evipal alone; and 6 patients were given evipal and morphine. One gram of evipal in 30 c.c. of tap water was given by rectum after the cervix was 3 cm. dilated. This was accompanied by 0.0004 Gm. of scopolamine hypodermically. There was no prolongation of labor. The results are reported as: Good, 70 per cent; fair, 14 per cent; and poor, 16 per cent. No definition of the evaluating criteria is given. The two series of evipal alone and evipal with morphine are too small for evaluation. Nine instances of fetal distress are cited. This seems high, although again the criteria for diagnosis are not stated.

L. M. HELLMAN.

Beruti, Josue A.: *Chloral Hydrate in Labor*, Arch. de la Clinica Obst. y Ginec. "Eliseo Cantón" 1: 58, 1942.

The author reports on ten years' experience with chloral hydrate used in 500 cases of prolonged or dystocic labors including (1) hyperdynamia, (2) hypertonia, (3) spasmodic contractions, (4) abnormal prolongation of labor because of slow dilatation, (5) physical and psychic exhaustion in protracted labor. The study was limited to an analysis of the relation between the medication used and the progress of labor as judged by uterine dilatation. In a large number of cases the results were negative or doubtful. The author believes that many of these failures are attributable to the use of insufficient dosage or administration at an inopportune time. In 28 cases the drug produced regulating and normalizing effects. In 15 of these cases the chloral hydrate was given in combination with other substances, generally "Spasmalgine." Four cases selected from the total series presented to the Society of Obstetrics and Gynecology of Buenos Aires and published in its bulletin, are given in condensed form. The author employs ingenious diagrams for recording the progress of dilatation, the administration of treatment, artificial or natural rupture of the membranes and expulsion of the fetus. The author concludes that chloral hydrate is, at times, extraordinarily effective in the correction and regulation of uterine dynamics and in the acceleration of dilatation; that it produces good results in certain cases of protracted labor and is a remarkable restorer of energy in cases of physical and psychic exhaustion. No deleterious effects on the mother or the child or on the progress of labor occur if the chloral hydrate enemas are not given too frequently and do not exceed doses of 3 Gm. There are no unfavorable effects on delivery or on the puerperium. In combination with "Spasmalgine," chloral hydrate frequently has a remarkably accelerating effect on cervical dilatation. It has often been observed that chloral hydrate, in moderate doses, is more efficient than "Spasmalgine" unless the latter is given in very large amounts, thus the hydrate is superior. Like other uterine depressants, antispasmodics or hypnotics, chloral hydrate often fails, presumably because it is given at the wrong time or in insufficient dosages.

J. P. GREENHILL.

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the indications for doing the operation and to point out where it fits into the scheme of obstetric operative procedures.

Technique

We have found the combination of nitrous oxide-oxygen-ether the best anesthetic for this operation. Cyclopropane, although given expertly for us, has not given satisfactory uterine relaxation for the extraction of the fetus. Much as we prefer local anesthesia, which we use almost routinely for our usual cesarean sections, we have not tried it for the extraperitoneal operation, chiefly because we feel that a patient who has had a protracted labor is not psychologically or physically adapted to its use.

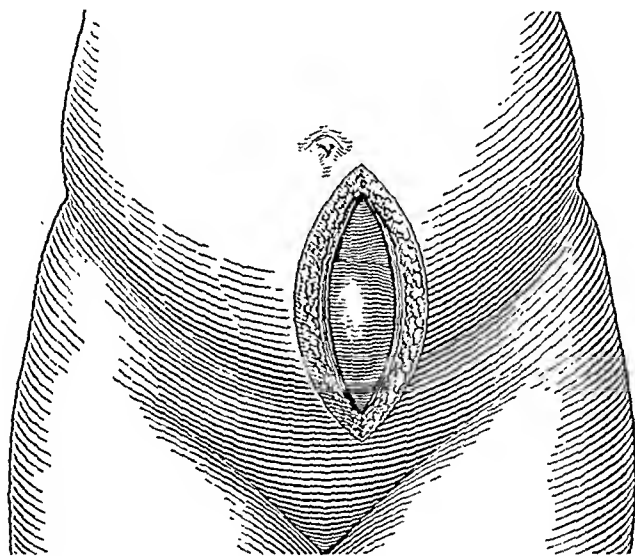


Fig. 1.—Left paramedial incision. Bladder is distended and the peritoneal cavity is in the upper angle of the wound.

After the patient has been anesthetized, a large catheter, preferably a No. 18 French, is introduced into the bladder and strapped with adhesive plaster to the right thigh in its middle third. The urine is then withdrawn. The catheter is then connected with a glass connecting tube attached to a long rubber tube which in turn is fitted to an infusion bottle containing 500 c.c. of sterile water. To this may be added 1 c.c. of a 5 per cent aqueous solution of methylene blue, the long rubber tube having a clamp near its attachment to the flask. This forms a closed system with a reservoir so that the bladder may be filled or emptied as desired by simply raising or lowering the bottle. The bladder is now filled with from 200 to 300 c.c. of sterile water, the amount varying with the height of the fundus of the bladder, the point being that the bladder should be easily visualized as a definite mound rising about three or four fingerbreadths above the symphysis pubis. The abdomen is now painted with whatever antiseptic one prefers and draped in the usual manner.

A left paramedian incision is now made, extending upward from the pubic tubercle for a distance of 15 cm. Although Latzko used a median suprapubic incision we prefer the paramedian which Küstner used originally. The fascia is incised and the left rectus muscle is separated in

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its middle by blunt dissection. The full field of operation is now in view and the peritoneal reflection should next be sought for and carefully inspected. The distended bladder fills the lower half of the incision (Fig. 1). The posterior rectus fascia and the fascia vesicae are now carefully opened with scissors along the left lateral wall of the bladder. These are not found as two distinct and separate layers, but rather as several layers of varying thickness which must be cut through before the bladder proper is reached. With a little experience this is readily recognized. These layers are then separated vertically by using the index finger of each hand for a blunt dissection, which is continued completely around the left lateral wall of the bladder to its posterior aspect, thus bringing the lower anterior uterine wall into view. The bladder is now emptied, by lowering the reservoir and clamping the long tube, and retracted far to the right by the use of a wide curved retractor, preferably the large curved blade of the usual Balfour type. A thin

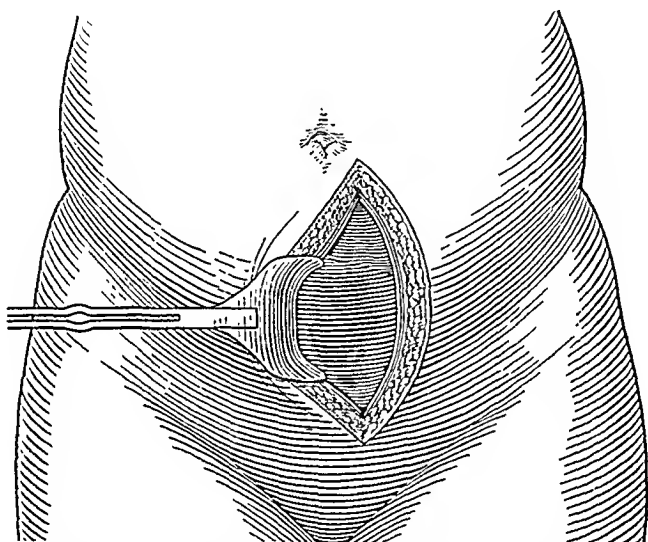


Fig. 2.—The bladder is emptied and retracted underneath the Balfour blade. Lower uterine segment is exposed. Peritoneum above.

layer of endopelvic fascia on the anterior surface of the uterus now comes into view. This thin layer of fascia is now incised vertically and the real peritoneal fold at the upper end of this fascia is pushed upward with it. Occasionally, especially if the patient has not been long in labor, the peritoneal fold comes down very low on the posterior aspect of the bladder, almost to the anterior lip of the cervix, and may be accidentally opened instead of the endopelvic fascia. This fascia should, therefore, be carefully inspected before the incision is made (Fig. 2). The uterus is incised by a vertical incision, but we have found that by curving the incision upward so that it is somewhat crescentic in outline, a much larger opening can be obtained for the extraction of the infant. The baby's head is now delivered by the use of the forceps, or by the posterior blade of the Barton forceps as a vectis, with the symphysis as a fulcrum. One cubic centimeter of pituitrin is now injected subcutaneously; also 1 c.c. of ergotrate is usually given. As many of our babies have been quite large, we have had some difficulty occasionally with their extraction, but this has never been serious.

The placenta usually presents itself in the wound spontaneously and is slowly extracted by making slight traction on the umbilical cord.

If the uterus shows a tendency to relax or if there is excessive bleeding, it is packed with ten or more yards of plain 2 inch gauze, half of which is removed in twenty-four hours and the remainder in forty-eight hours. The uterine incision is sutured in two layers, the first a double No. 1 chromic catgut continuous in the muscle, and the second a single continuous No. 1 chromic catgut of the Cushing type in the fascia. The wound is now inspected and any bleeding points caught and ligated. The bladder is then refilled to make certain that it has not been accidentally injured, and the peritoneum is also carefully inspected for any accidental openings. A Penrose drain is inserted behind the bladder over the uterine incision. Recently we have been placing from 4 to 12 Gm. of sulfathiazole powder behind the bladder over the uterine incision, prior to placing the drain. The bladder is allowed to fall back in its natural place and is not sutured into position. The rectus muscle is approximated with a few interrupted No. 1 plain catgut sutures and the fascia is sutured with a continuous No. 1 chromic catgut. The skin is closed with either silkworm-gut or Michel clips. Retention sutures are used by some of us. The catheter is allowed to remain in situ for twenty-four hours, being attached to a drainage bottle. The wound has to be dressed after twenty-four hours, as there is usually considerable sero-sanguineous drainage during this period. It is greatly diminished in the next twenty-four hours. The Penrose drain is shortened in forty-eight hours and removed in seventy-two hours.

Analysis of Cases

Age.—Fifteen of our patients were thirty years of age or over, the oldest being a primigravida, age 40; the remaining ten varied in age from 21 to 30.

Parity.—All patients, with one exception, a para I, were primigravidas.

Temperature at the Time of Operation.—Eight of our patients had a temperature of 100° F. (37.7° C.) or over at the time of operation, the maximum being 104.4° F. (40.2° C.).

Period of Gestation.—All patients were at term, with one exception, thirty-five weeks' gestation.

Cultures From Uterus or Placenta.—Cultures were made in 10 cases but in none was the beta hemolytic streptococcus found.

Injuries to Peritoneum or Bladder.—In eight instances the peritoneal cavity was accidentally opened, but in each instance the rent was immediately repaired with fine plain catgut. There were no injuries to the bladder. Beginning in 1941 in four cases sulfathiazole or sulfanilamide was used, in amounts varying from 4 to 12 Gm., the latter amount being used in the patient with a temperature of 104.4° F. (40.2° C.) at the time of operation.

Morbidity.—The morbidity standard which we have employed is a rise of temperature to 100.4° F. (38° C.) or over at any time excluding the first seventy-two hours after operation. By this standard fourteen patients were nonmorbid. The causes of the morbidity in the remaining cases were as follows:

1. Temperature varying from 100° to 102° F. (37.7° to 39.9° C.) eighth to nineteenth day. Thrombophlebitis right femoral vein, discharged twenty-ninth day.



livered, there was one stillbirth, the baby being known to be dead at the time of the operation, and one fetal death, the latter being a baby upon whom a forceps delivery had been attempted. It died shortly after birth of a cerebral hemorrhage (proved at autopsy). The smallest was delivered by a breech extraction and suffered a slight injury to the right leg from the traction upon this extremity.

Private and Ward Patients.—Of the 25 patients operated upon, 21 were private patients and four were service patients, although the service patients constitute about 40 per cent of all the patients delivered at the hospital.

Operating Time.—The operating time varied from thirty to seventy-five minutes, the average time being forty-five minutes.

Transfusions.—Four patients were transfused immediately after operation.

Classification of Pelves.—In thirteen instances the pelvis was stated to be ample. Six patients were x-rayed by the Caldwell-Moloy method. The final classifications of the pelves were as follows:

Clinically	{ Ample	13
	{ Simple flat	2
	{ Funnel (male)	3
	{ Generally contracted	1
		<hr/> 19
By x-ray	{ Small gynecoid	2
	{ Android	1
	{ Android flat	1
	{ Anthropoid	1
	{ Asymmetrical	1
		<hr/> 6

Operators.—Twenty-four of the patients were operated upon by five members of the obstetric staff, the remaining patient by the attending gynecologist.

Blood Loss.—The blood loss was estimated in each instance. In only seven instances was it considered to be 500 c.c. or over, the highest being 1,200 c.c. in one instance.

Packing.—In 13 instances the uterus was packed.

Wound Infections.—In only 3 instances were there wound infections of any gravity.

Postoperative Distention.—The convalescence from the operation was remarkably smooth in every instance, undoubtedly due to the extraperitoneal character of the operation. Postoperative distention was described as marked in only four instances, in only 2 of which was suction treatment required (Wangensteen).

Catheterization.—At first we allowed the catheter to remain in the bladder several days but recently we have been removing the catheter within twenty-four hours. In no instance have we had to resort to catheterization, and there has been a marked absence of bladder symptoms.

Summary

Our results with 25 Latzko extraperitoneal operations have been gratifying. We realize that the operation competes with (1) delivery per vaginam usually by difficult instrumental delivery, extensive laceration

2. Temperature varying from 100° to 103.6° F. (37.7° to 39.6° C.) until twenty-first day. Thrombophlebitis right cubital and left femoral vein. Wound infection. Discharged thirty-first day.

3. Temperature varying from 100° to 102.6° F. (37.7° to 39.2° C.) for six days. Wound infection. Discharged eighteenth day.

4. Temperature 103° F. (39.4° C.) day of operation, 100° to 103.6° F. (37.7° to 39.6° C.) for six days. Endometritis. Discharged fourteenth day.

5. Temperature varying from 98.6° to 101° F. (37° to 38.3° C.) for eight days. Endometritis. Discharged fifteenth day.

6. Temperature varying from 100° to 102° F. (37.7° to 38.9° C.) for seven days. Endometritis. Discharged twenty-first day.

7. Temperature varying from 100° to 102.6° F. (37.7° to 39.2° C.) for ten days. Endometritis. Discharged fourteenth day.

8. Temperature varying from 98.6° to 101.6° F. (37° to 38.6° C.) for seven days. Endometritis. Discharged seventeenth day.

9. Temperature varying from 99.6° to 102° F. (37.5° to 38.9° C.) for twelve days. Endometritis. Discharged twentieth day.

10. Temperature varying from 98.6° to 103.6° F. (37° to 39.6° C.) for eighteen days. Severe wound infection. Discharged twenty-fifth day.

11. Temperature varying from 98.6° to 100.4° F. (37° to 38° C.) for seven days. Thrombophlebitis left femoral vein. Discharged twenty-second day.

Length of Stay in Hospital.—Nineteen patients were discharged between the eleventh and eighteenth days. Six remained in the hospital from eighteen to thirty-one days. Only one remained thirty-one days due to a thrombophlebitis of the right cubital vein following intravenous therapy.

Hours of Labor.—Except for one patient who was in labor only nine hours, all had been in labor from nineteen to seventy-eight hours, and of these, 16 had been in labor thirty-six hours or more. The membranes were intact in only two instances, and in the remaining 23 the membranes had been ruptured from two hours to eleven days.

Condition of Cervix.—Dilatation of the cervix varied from 1 finger, as in the case with severe amniotic sac infection with a temperature of 104.4° F. (40.2° C.), to full dilatation. In the majority of cases, however, after prolonged labor with ruptured membranes, the cervix was partially dilated (2 fingers) and was described as thick, rigid, or edematous in 15 instances.

Rectal and Vaginal Examinations.—Rectal examinations were done in all cases, the number varying from one to thirteen. One or more vaginal examinations were done in 19 cases, the maximum number being four, in a patient upon whom forceps delivery had been attempted. Forceps delivery had been attempted in three instances and the insertion of a Voorhees bag had been employed in one instance, a breech presentation with rupture of the membranes for a long time and no labor.

Position.—It is interesting to note that in 18 instances the position was occiput posterior or transverse. In three patients the breech presented and in only four instances was the position anterior.

Weights.—The smallest baby weighed 4 pounds (2,220 Gm.); the largest 9 $\frac{3}{16}$ pounds (4,475 Gm.).

Deaths (Fetal).—The operation was done ten times in the interest of the baby and in all, except one known intrauterine fetal death, the interests of the baby and mother were paramount. Of the 25 babies de-

type operations. In a ten-year period to Jan. 1, 1942, we delivered 53,616 women. There were 171 deaths or 0.34 per cent. In this number there were 1,432 cesarean sections, an incidence of 2.67 per cent. There were 28 deaths, a mortality of 1.9 per cent. Two hundred and eighty-six extraperitoneal operations were performed of different types, with 4 deaths, or 1.74 per cent. One hundred and ninety-two operations of the supravescical type which I described were performed, with 2 deaths or 1.04 per cent (no mortality corrections).

It is evident from the foregoing that we are in accord with Drs. Williamson and Goldblatt concerning the safety and utilization of any good extraperitoneal operation for actually or potentially infected patients.

DR. WILLIAM E. STUDDIFORD.—We have restricted extraperitoneal operations at Bellevue Hospital to cases in which very definite indications are present. I have reviewed our cesarean sections for the past five years. There were 164 sections performed during that period among 7,589 obstetric patients, an incidence of 2.2 per cent. The general maternal mortality during that time was 2.9 per thousand. Five patients died following cesarean section, a mortality rate of 3 per cent, 10 times greater than the general mortality. Of these cases, 84 were operated upon, most of them following the onset of labor, by transperitoneal low flap cesarean section through the lower segment. In this group there were two deaths, a mortality of 2.4 per cent, but one of these fatalities was in a patient with carcinoma of the rectum, who died fourteen days following the operation. At autopsy it was found that her death was in no way related to the operation. That leaves one death in this group and a corrected mortality of 1.2 per cent, which is comparable but slightly more than the mortality which Dr. Waters has reported for extraperitoneal operations. Furthermore, in studying the single remaining fatal case it was found that the patient had had cyclopropane anesthesia, that a tightly contracted uterus prevented dislodgment of the head from the pelvis, and that the operator extracted the baby as a breech, extending the lower segment incision into the body of the uterus. If this had been done with an extraperitoneal operation, the same disastrous result might well have been expected.

There were 67 classical operations with only one death, a mortality of 1.5 per cent. This case was one of complete separation of the placenta before term, with a long, thick cervix, and I doubt whether we would have thought of attempting the extraperitoneal route. This patient died of peritonitis, for which we were unable to assign a cause since she did not have ruptured membranes and was not in labor.

Ten of these cases had a Porro operation with no deaths. I would disagree with Dr. Waters as to discarding that procedure. Two of these patients had ruptured uteri. One patient with 3 living children had a contraction ring with a dead fetus and an infected uterus. One was a patient with a placental separation, in which the uterus did not react. Three had large fibroids, in one instance the tumor weighing 16 pounds and the baby 6½ pounds. One was a hydatid mole in a woman of 40 years, who was six and one-half months pregnant. One had a macerated fetus with an infected amniotic sac, again a woman of 40 who had four living children. Repeated effort to induce labor had failed.

Finally the group of extraperitoneal sections number only 3, one by the lateral approach and two by the supravescical approach. There were two deaths in this group. I think it may be worth while to say a little about the two patients who died. Both of them were in labor for several days, had antepartum fever and were seriously sick. One patient, operated upon by the supravescical approach, died of an exsanguinating hemorrhage occurring immediately after the extraction of the fetus, the uterus being completely atonic. I believe that in this case it is probable that the only operation which would have met with success would have been a Porro. In the second case the peritoneum was accidentally entered, but it was sutured before the uterus was opened. The patient developed an extensive wound infection; the entire

tion of the soft parts and probable fetal death, (2) a low flap transperitoneal cesarean section, and (3) a Porro cesarean section. As we review our cases no doubt some of these patients could have been delivered by a low flap cesarean section, but the risk to the patient's life would have been, in our opinion, greatly increased. Some of these patients could have been successfully treated by a Porro operation, but that would have meant the loss of the childbearing function in a primigravida. On the other hand, we have found this operation to be of the greatest value for patients when it is desirable to give a true test of labor; where tentative attempts at instrumental delivery have been made, or, when during the course of labor, with ruptured membranes, a severe amniotic infection becomes manifest more or less suddenly. It has been a source of satisfaction to us to feel that our patients could survive and that the postoperative course would be quite smooth, and that the baby has a much better chance of survival. In the type of patient upon whom the operation was performed no other obstetric procedure could give us this confidence as to the outcome of both mother and baby.

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Discussion

DR. EDWARD G. WATERS.—We do the Latzko operation at the Margaret Hague Maternity and about one out of five of our extraperitoneal cesarean sections is still done by that approach.

There are really only two extraperitoneal approaches to the lower uterine segment. One is the *paravesical* approach which was first proposed by Joerg in 1809, and first attempted by Ritgen, and afterwards most effectively by Latzko, to whom major credit for that type of approach should be given. While Latzko's abdominal approach is unique, a paravesical approach had been proposed and attempted a century earlier, but his operation is by far the best of the paravesical operations.

The *supravesical* approach was proposed by Physick to Dewees but never performed by either. However, it was unsuccessfully attempted by Sellheim and by Frank who missed the "anatomic plane."

The extraperitoneal operation is an old story in Europe. As a matter of fact, I was rather surprised to find that Bumm and Doederlein compiled 444 extraperitoneal approaches to the lower uterine segment with a mortality of about 5.6 per cent, which is excellent. That was some years ago.

Our opinion is based upon the fact that we have done more than 200 extraperitoneal cesarean sections of the type I described with but 2 deaths. For potentially and actually infected cases, the mortality is lower than our general mortality for over 1,500 cesarean sections of all types. It is lower than any appreciable series reported on Porro operations. It is somewhat lower than in our own experiences with Latzko

DIRECT MEASUREMENT OF CALDWELL-MOLOY X-RAY PLATES

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X-RAY pelvimetry is assuming increasing importance as an aid in the scientific practice of obstetrics. It is helping in making labor safer because it permits one to estimate pelvic capacity and also to anticipate the mechanism of labor in the majority of cases.

Thoms has stated, "The older methods of estimating pelvic capacity are unreliable even in experienced hands, and the loss of a baby through untimely operative procedures, or of a mother through delayed cesarean section may occur in these same hands as a result of inexact knowledge of pelvic capacity." Although there is no doubt that trained obstetricians gain a great deal from the clinical evaluation of the pelvis, they have now accepted the fact that x-ray assistance in diagnosis should not be neglected.

The work of Caldwell and Moloy in the interpretation of pelvic architecture is one of the great contributions to the field of obstetrics. If a hospital has a precision stereoscope and a technician trained to take the required films, this method of comparing the relative sizes of the pelvis and the fetal head is the most scientific at our disposal.

Some obstetricians study only architecture and consider measuring the pelvis unnecessary. We believe that measurements present additional information especially important in the borderline pelvis. If the obstetric conjugate, for example, is less than 9 cm., a difficult delivery may be anticipated even in a true gynecoid pelvis. Although Heaton has shown that the number of absolute contractions is relatively small, the number of borderline pelvises is comparatively large. This type which so often presents a serious obstetric problem can best be evaluated by clinical examination and x-ray study of both architecture and measurements.

The limitations of x-ray pelvimetry have long been recognized. It should never be regarded as replacing clinical examination, mature judgment, and obstetric experience. The science and art of obstetrics cannot be reduced to a mere mechanical process. There are too many factors which cannot be translated into mathematical terms.

We believe that measurements should be to obstetrics what a leucocyte count is to the "surgical abdomen." If they conform with the clinical picture, they present additional support for the treatment to be followed. On the other hand, if a test of labor is indicated on the basis of the obstetrician's clinical judgment, the measurements should not deter this procedure.

abdominal wound broke down, the muscles and fascia sloughed and about five days postoperatively she developed generalized peritonitis.

I would like to emphasize that it is probable that this type of operation, even with its extraperitoneal approach, has certain dangers in severely infected patients and should not be regarded as one to be undertaken with complete safety regardless of the condition of the patient.

DR. WILLIAM LATZKO.—Thirty-four years ago when I first performed and published the extraperitoneal cesarean section, the classical type of procedure was limited to absolutely clean cases. The extraperitoneal section aimed at the extension of the indication to potentially infected cases without too great a risk. But I learned from the articles published by American obstetricians that it was possible to extend this indication moreover to cases which were not only potentially but actually infected, as proved by bacteriologic examinations or by clinical symptoms. This was a risk which neither I myself nor other European obstetricians had dared to take.

I would like to state that, in my opinion, this extension of the indications has been the greatest step forward in the whole question. I believe that no modification of the operative technique can equal the progress which has been made thereby.

DR. ERWIN F. SMITH.—A majority of obstetricians today feel that an extraperitoneal cesarean section well done by a competent operator is safer than a transperitoneal procedure.

From my experience in approximately 50 true extraperitoneal cesarean sections, as distinguished from, and not to be confused with, the peritoneal exclusion operation, which I published, I have found that the postoperative comfort of the patient in most of these cases, especially the electives, has been decidedly better as compared to that of my concurrent classicals and low flap operations.

The sulfonamides should make it doubly safe in infected cases. Therefore, it has been my policy to use the extraperitoneal technique in every cesarean section, unless contraindicated, and thereby give the patient the benefit of this postoperative comfort.

DR. HERVEY C. WILLIAMSON.—We have done four more Latzko type operations since this paper was prepared. We gave no statistics for the French Hospital on the total number of cesarean sections. In the first 7,500 deliveries there were 305 cesarean sections of all types with but two maternal deaths. One was a patient with severe toxemia. She died the next day of a cerebral hemorrhage and, curiously, an autopsy showed typical eclampsia. The other patient died of peritonitis.

We agree with Dr. Burns and have reserved this operation for patients long in labor. We also agree with Dr. Studdiford that some of these patients could undoubtedly have had a flap operation. However, we feel, as Dr. Smith does, that this operation is safer and that the patients have a smoother convalescence.

I have seen Dr. Waters do his operation. It seemed to me that if we freed the upper left hand angle of the bladder a little more and curved the incision transversely instead of vertically, we would be doing the same operation. Our approach, however, is slightly different.

TABLE I. CORRECTION TABLE FOR DISTORTION
MEASUREMENT FROM PLANE TO BASELINE OF RULER IMAGE OF LATERAL FILM

	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
4.0	3.5	3.4	3.4	3.3	3.2	3.2	3.1	3.1	3.0	2.9	2.9	2.8	2.8	2.7	2.6
4.5	3.9	3.8	3.8	3.7	3.6	3.5	3.4	3.4	3.3	3.2	3.2	3.1	3.1	3.0	2.9
5.0	4.4	4.2	4.1	4.0	3.9	3.8	3.7	3.7	3.6	3.5	3.5	3.4	3.4	3.2	3.1
5.5	4.8	4.6	4.5	4.4	4.3	4.2	4.1	4.0	3.9	3.8	3.8	3.7	3.6	3.5	3.4
6.0	5.3	5.0	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1	4.0	3.9	3.8	3.7
6.5	5.7	5.5	5.3	5.2	5.1	5.0	4.9	4.8	4.7	4.5	4.4	4.3	4.2	4.1	4.0
7.0	6.2	5.9	5.8	5.6	5.5	5.4	5.3	5.2	5.1	4.9	4.8	4.7	4.6	4.4	4.3
7.5	6.6	6.3	6.2	6.0	5.9	5.8	5.7	5.6	5.5	5.3	5.2	5.0	4.9	4.7	4.6
8.0	7.1	6.8	6.6	6.4	6.3	6.2	6.1	6.0	5.9	5.7	5.6	5.4	5.3	5.1	4.9
8.5	7.5	7.2	7.0	6.9	6.8	6.7	6.5	6.4	6.3	6.1	6.0	5.8	5.7	5.5	5.3
9.0	7.9	7.7	7.5	7.4	7.2	7.1	7.0	6.9	6.7	6.5	6.4	6.2	6.1	5.9	5.7
9.5	8.3	8.1	7.9	7.8	7.7	7.5	7.4	7.3	7.1	6.9	6.8	6.6	6.5	6.3	6.1
10.0	8.8	8.6	8.4	8.2	8.1	7.9	7.8	7.7	7.5	7.3	7.2	7.0	6.9	6.7	6.5
10.5	9.2	9.0	8.9	8.7	8.5	8.3	8.2	8.1	7.9	7.7	7.5	7.3	7.2	7.0	6.8
11.0	9.6	9.4	9.3	9.1	8.9	8.7	8.6	8.5	8.2	8.0	7.9	7.7	7.5	7.3	7.1
11.5	10.1	9.9	9.7	9.5	9.4	9.1	8.9	8.8	8.6	8.4	8.2	8.0	7.8	7.6	7.4
12.0	10.5	10.3	10.1	9.9	9.8	9.5	9.3	9.2	8.9	8.7	8.6	8.4	8.2	8.0	7.8
12.5	10.9	10.7	10.5	10.3	10.2	9.9	9.7	9.5	9.3	9.1	8.9	8.7	8.5	8.3	8.1
13.0	11.4	11.2	10.9	10.7	10.6	10.2	10.0	9.9	9.7	9.4	9.2	9.0	8.9	8.6	8.4
13.5	11.8	11.6	11.4	11.1	11.0	10.6	10.4	10.3	10.1	9.8	9.6	9.4	9.2	9.0	8.8
14.0	12.2	12.1	11.8	11.6	11.4	11.0	10.8	10.6	10.4	10.1	10.0	9.8	9.6	9.3	9.1
14.5	12.7	12.5	12.2	12.0	11.8	11.4	11.2	11.0	10.8	10.5	10.3	10.1	9.9	9.7	9.4
15.0	13.1	12.9	12.6	12.4	12.2	11.8	11.6	11.4	11.2	10.9	10.7	10.5	10.3	10.1	9.8
15.5	13.5	13.4	13.1	12.9	12.7	12.2	12.0	11.8	11.5	11.2	11.1	10.8	10.6	10.4	10.1
16.0	13.9	13.8	13.5	13.3	13.1	12.6	12.4	12.2	11.9	11.6	11.4	11.2	11.0	10.8	10.4
16.5	14.4	14.2	13.9	13.8	13.5	13.0	12.8	12.6	12.3	12.0	11.8	11.6	11.4	11.1	10.8
17.0	14.9	14.6	14.3	14.2	13.9	13.4	13.2	13.0	12.7	12.3	12.2	12.0	11.8	11.5	11.1
17.5	15.3	15.0	14.7	14.6	14.3	13.8	13.6	13.4	13.1	12.7	12.5	12.3	12.1	11.8	11.4
18.0	15.7	15.5	15.1	14.9	14.6	14.2	14.0	13.8	13.5	13.1	12.9	12.6	12.4	12.1	11.7

Transverse Measurement in Centimeters on
Anteroposterior Film

The following measurements are generally accepted as borderline for the passage of the average size baby:

Obstetric conjugate	8.5-9.5 cm.
Interspinous	8.5-9.5 cm.
Posterior sagittal of midplane	4 cm.
Bitrochanteric	8.5-9.0 cm.
Posterior sagittal of outlet	6 cm.

The following measurements indicate absolute contraction for passage of an average size baby:

Obstetric conjugate	8-8.5 cm.
Interspinous	8 cm.
Posterior sagittal of midplane	3.0-3.5 cm.
Bitrochanteric	8 cm.
Posterior sagittal of outlet	5 cm.

Many find it difficult to measure accurately the planes of the pelvis through the stereoscope. Variations of centimeters in the readings of several obstetricians for the same films have often been noted.

We, therefore, sought a method to act as a check which would not depend on individual ocular differences. This was accomplished by modifying the procedure introduced by one of us (Graber) to apply to films taken with the Caldwell-Moloy technique. It has the added advantage of not necessitating the use of a precision stereoscope. Any available type is suitable for the study of architecture and measurements are taken directly from the x-ray films.

The routine method of taking Caldwell-Moloy films, is followed. The only additional equipment necessary is a metallic ruler 18 cm. long which has been notched at $\frac{1}{2}$ cm. intervals. This is placed between the patient's buttocks when the lateral plate is taken.

The measurements of all midline diameters directly on a ruler placed in the midline is obvious and has been utilized in many of the advocated methods of x-ray pelvimetry.

Determination of transverse measurements is based on the geometric theorem "*In similar triangles, the bases bear the same relationship to each other as do the altitudes.*"

Technique

Inasmuch as the metallic ruler lies in the midline, its image on the lateral film will be distorted (enlarged) in the same proportion as are all midline measurements. To measure any anteroposterior diameter, the distance between its landmarks is taken, transposed to the image of the ruler and the true measurement is obtained. In Fig. 1, *AB* measured in cm. on the ruler image gives the reading for the true conjugate, *CD* the posterior sagittal of the midplane, and *ED* the posterior sagittal of the outlet.

For the transverse measurement of any plane, measure the distance in centimeters between its landmarks directly from one of the anteroposterior (stereoscopic) views (Fig. 2). These transverse diameters of the inlet (*MN*), midplane (*OP*), and outlet (*RS*) lie at different distances from the x-ray tube and the degree of distortion for each is different.

It may be noted that rotation of the pelvis in the anteroposterior view may result in an error of 0.1 to 0.2 cm., but this is not of obstetric significance. We have checked this method and have found it accurate to 0.5 cm. or less.



Fig. 2.—*MN*, Widest transverse of inlet; *OP*, bispinous; *RS*, bituberous.

In conclusion, we should like to emphasize the fact that the pelvis is only one of the factors in the process of labor. The others cannot be replaced by numerical equivalents, and therefore the correct mathematical answer may not be the correct obstetric solution. Nevertheless, we believe that x-ray mensuration of the pelvic planes is a valuable aid in the practice of obstetrics.

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To determine the degree of distortion of each, the lateral view is again consulted. A true baseline is drawn parallel to the film edge and just touching the outer border of the sacrum (*GH*). A line is then drawn from a point between the ischial spines perpendicular to the true conjugate (*CF*). The point of crossing divides this conjugate into anterior and posterior sagittals and represents the location through which the transverse of the inlet plane will pass. The shortest distance from this point to the baseline (*FJ*) is measured on the ruler image for correction.

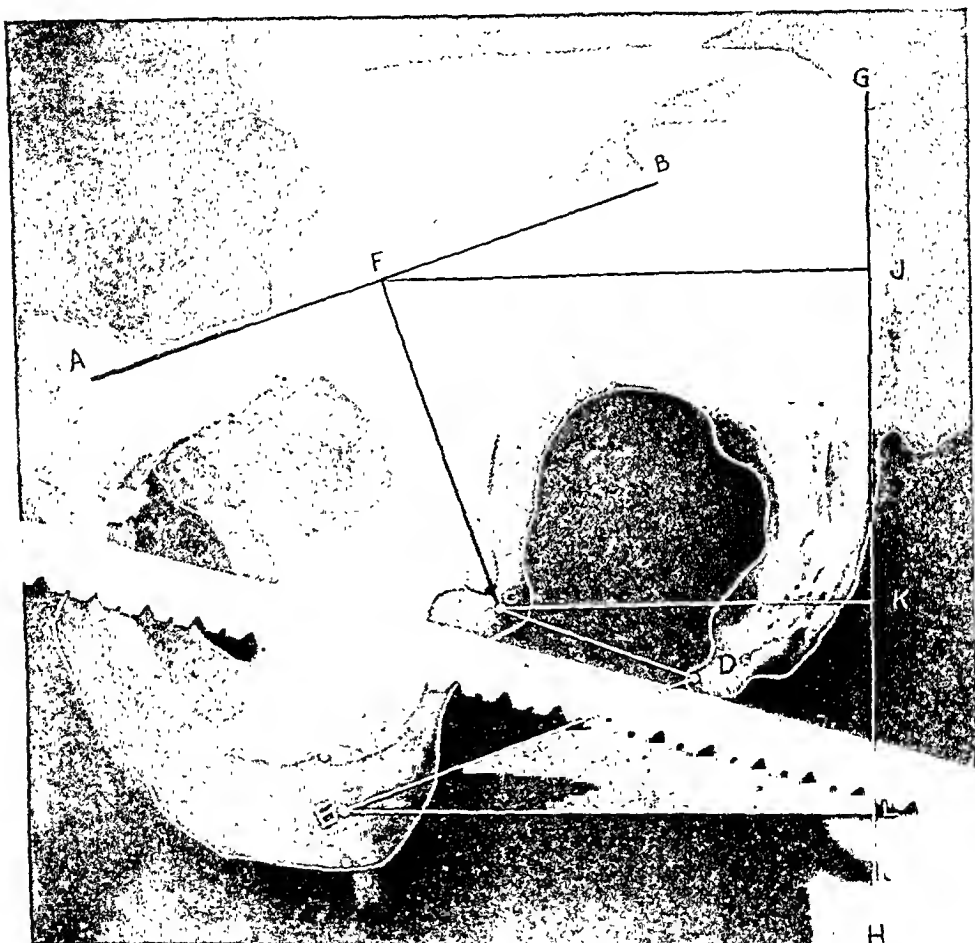


Fig. 1.—*AB*, Obstetric conjugate; *CD*, posterior sagittal of midplane; *ED*, Posterior sagittal of outlet; *GH*, baseline parallel to film edge touching sacrum; *CF*, perpendicular from spines to obstetric conjugate; *FJ*, distance from transverse of inlet to baseline; *CK*, distance from ischial spines to baseline; *EL*, distance from bituberous to baseline.

For the interspinous correction, the distance from the midpoint between the two spines and the baseline (*CK*) is measured on the ruler image.

For the transverse of the outlet, the distance from the midpoint between the tuberosities to the baseline (*EL*) is measured on the ruler image.

Thus two figures are obtained for each transverse diameter, the direct reading from the anteroposterior stereoscopic view and its corrected distance from the baseline from the lateral view. These are referred to the table of correction and the true transverse measurements are obtained (Table I).

TABLE I. WEIGHT LOSS OF BABIES

	PERIOD OF NO VISITING RESTRICTIONS	PERIOD OF VISITING RESTRICTIONS	DIFFERENCE
Initial weight loss (Gm.)	308.7	229.4	79.3
Average Gm. below birth weight at discharge	81.2	37.7	43.5
Per cent regaining birth weight at discharge	27.0	41.1	14.1

with only 27 per cent in the former group. These differences are significant when one considers that most babies in both groups had comparable weight variations and that these average figures are the result of much greater weight difference in a smaller group of babies. The smaller group of infants who have lost more and gained less are those babies who make up the inevitable feeding problems. The ones most susceptible to all infant diseases and infections are the babies who have the greatest need for an adequate breast supply.

TABLE II. DAILY MILK CONSUMPTION

	PERIOD OF NO VISITING RESTRICTIONS	PERIOD OF VISITING RESTRICTIONS	DIFFERENCE
Average amounts of breast milk (daily) at discharge	499.3 c.c.	556.0 c.c.	56.7 c.c.

In Table II are listed the average twenty-four-hour outputs of breast milk in the two groups of mothers. The figures tend to confirm the more satisfactory feeding of infants by undisturbed mothers. The mothers who did not suffer the distractions and mental exertions of entertaining the sewing circle or bridge club were able to produce the greater breast supply.

TABLE III. PERCENTAGE OF BABIES ON ARTIFICIAL AND COMPLEMENTARY FEEDINGS

	PERIOD OF NO VISITING RESTRICTIONS	PERIOD OF VISITING RESTRICTIONS	DIFFERENCE
Per cent of infants receiving artificial feedings	12.0	12.0	0.0
Per cent of infants receiving complementary feedings	22.0	4.0	18.0

There apparently is a certain percentage of women who are totally unable to nurse, either because they selfishly refuse to try, or because of a systemic disease which precludes nursing, or because of a primary agalactia. Weiss and Hölzel state that it is generally recognized that agalactia of a primary nature is a rare experience. More frequently there is a variable degree of primary hypogalactia. Benoit has said that 90 per cent of infants should be breast fed on leaving the hospital, and the writers feel that by repeated emphasis on the benefits of breast

THE IMPORTANCE OF REST IN THE INITIATION OF BREAST FEEDING

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ALTHOUGH the benefits of breast feeding newborn babies have been repeatedly stressed by a number of writers, need for emphasizing this physiologic and important function continues. We had the opportunity, during 1941, to make some interesting observations concerning the possible effect of rest and isolation on nursing mothers. During the encephalitis epidemic, all visitors except husbands of patients were banned from the maternity floor of St. Luke's Hospital. It was noted in that period that a fewer number of mothers failed to furnish a complete supply of breast milk for their babies; the authors studied the records of the last 100 patients delivered during this restriction and compared the results with 100 consecutive cases selected earlier in the year as a control group. Even in the control group a large percentage of babies left the hospital supplied by maternal feedings entirely. The authors have always stressed the importance of nursing, and mothers were given every encouragement to follow this normal function and procedure.

Discussion of Data

Before one attempts to evaluate the more significant statistical data (obtained from this study), he should note that all factors, other than visiting restrictions, which might be expected to influence lactation, were approximately equal in both groups of patients. All patients were discharged on the ninth or tenth day, as a rule. Average age and parity were the same. Maternal morbidity was 3 per cent in each group. There was a slightly lower incidence of operative deliveries in the control cases. It might also be pertinent to mention that the infant morbidity consisted of 3 cases of impetigo, all occurring among the controls. The authors attribute in part the high percentage of nursing mothers to the fact that they are in close association with a pediatrician who recognizes the value of mother's milk.

From Table I one notes that the babies delivered before the visiting restrictions were inaugurated suffered a definitely greater initial weight loss and were further under birth weight at the time of discharge than the babies delivered after the ban was inaugurated. This conclusion is reflected in the fact that 41 per cent of the latter group of infants regained their birth weight at the end of nine or ten days, as compared

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VITAMIN B IN HEARTBURN OF PREGNANCY*

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(From the University of Louisville Clinics)

SIXTEEN prenatal patients complained of annoying heartburn with a duration of from two days to two months, and on an average of two weeks. All but three were in the last half of gestation. The usual treatment of alkalies, as used in nonpregnant individuals, proved notably inefficient when tried.

Two of the group had previously had clinical pellagra, and they attributed their symptoms to this. They were given large doses of the B complex in the form of a yeast extract plus 200 mg. of nicotinic acid daily. They were completely relieved of all symptoms but were kept on smaller maintenance doses throughout their pregnancies. Each was approximately seven months pregnant when first seen.

Of the remainder of the patients, one received a TRN6P† tablet after meals and was relieved of a heartburn of two months' standing within one week. Four patients received 200 mg. of nicotinic acid a day for a week, divided into four doses. One patient was relieved and the other three were unchanged. They were then given thiamin chloride, 50 mg. intravenously, followed by 25 mg. a day, orally. One had complete relief, one was partially relieved, and one remained unchanged. Nine patients all received thiamin chloride as the initial medication. Two received only one dose of 50 mg., intravenously, and no further treatment. One reported partial relief while the other was unchanged. Four received 25 mg. daily, orally, after the initial dose of 50 mg. intravenously. All reported complete relief in one to four days. One patient was not given an initial intravenous dose but received 25 mg. orally, twice a day. She was relieved after two days.

The two remaining patients were in the hospital. One had a pyelitis at five months' gestation and was given sulfathiazole. She complained of severe heartburn on the second day of this medication. Alkalies gave little relief. On the fourth day she was given 50 mg. of thiamin chloride intravenously, and 25 mg., twice a day, orally, thereafter. She had partial relief in forty-eight and complete relief in seventy-two hours. The sulfathiazole was continued throughout and no alkalies were given after the thiamin was begun. The other patient who was hospitalized

*Read at a meeting of the Louisville Obstetrical and Gynecological Society January 26, 1942.

†TRN6P is an experimental vitamin preparation of Merck and Co. It contains thiamin 5 mg., nicotinamide 25 mg., pyridoxine 5 mg., riboflavin 5 mg., and pantothenic acid 25 mg., per tablet.

feeding they have approached the approximate limit of 90 per cent for several years. Consequently, the restriction of visitors has made no significant change in the group of babies receiving artificial feedings, as borne out in Table III.

There are, however, less than one-fifth as many infants discharged with complementary feedings necessitated by inadequate milk supply as formerly. Note that the authors do not use complementary feedings for full-term infants during the first three days or at any other time unless the condition of the mother indicates some degree of hypogalactia. This emphasizes the apparent fact that the physical and mental fatigue induced by the efforts of the patient to entertain her visitors has the result of reducing the breast supply below the point of adequacy. Those same mothers, well rested in the hospital, might never have had to bother with the tasks of formula making plus breast feeding. This benefit is all the more significant in the light of the generally recognized fact that once a baby is well started on a complementary bottle, it often ends up on the bottle alone.

TABLE IV. PERCENTAGE OF MOTHERS WHO NURSED COMPLETELY OR PARTIALLY

	PERIOD OF NO VISITING RESTRICTIONS	PERIOD OF VISITING RESTRICTIONS	DIFFERENCE
Mothers able to nurse with no complementary feeding	66.0	84.0	18.0
Mothers able to nurse with complementary feeding	22.0	4.0	18.0
Total mothers who nursed completely and partially	88.0	88.0	0.0

Table IV emphasizes the facts that certain mothers are totally unable to nurse and that complete rest eliminates the use of complementary bottles for many patients.

Conclusions and Summary

1. The advantages of breast feeding for both infant and mother have been re-emphasized.
2. The records of 100 consecutive babies delivered during a period in which visitors were banned are compared with those of 100 consecutive cases delivered when no such restrictions were in force.
3. Infants delivered of mothers not disturbed by visitors more frequently regained their birth weight at discharge and suffered a smaller initial weight loss.
4. Undisturbed mothers had a more abundant supply of breast milk.
5. Although the percentage of artificial feedings was unchanged, the percentage of complementary feedings was reduced four-fifths by the restrictions.
6. Visiting restrictions must be taken into account when the physician considers the problem of instituting breast feedings.

These results suggest the possibility that the low acidity was due to nicotinic acid deficiency in that both patients had a prompt increase in acid after being given nicotinic acid. This phenomenon does occur in many pellagrins who have low gastric acidity at the beginning of treatment.

The majority of the patients with heartburn during pregnancy responded to vitamin B in rather large doses. The most important component was the thiamin. However the titer of the hydrochloric acid in the stomachs of two patients remained low until they were given nicotinic acid.

I wish to acknowledge the advice of Drs. V. P. Sydenstricker and Richard Torpin of the University of Georgia in the early phases of this work.

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Addendum

Ten additional patients from private practice have been treated. Four were taking small doses of vitamin B complex which did not prevent the onset. All received an initial dose of 50 mg. of thiamin chloride intravenously and 30 mg. daily by mouth. Five were given two additional intravenous doses at two-day intervals. Three were not benefited after a week. Two of these were then given an ampoule of suprarenal cortex subcutaneously at the time they received a fourth intravenous dose of thiamin and reported considerable relief. This might be explained on the basis of experiments which show that suprarenal cortex increases the activity of thiamin chloride.

was at six months' gestation. Her complaints were severe nausea, vomiting, and heartburn of six days' duration. She was given thiamin, 50 mg. twice a day, intravenously, and no other treatment, except what fluids she could take by mouth. She was partially relieved in twelve hours and completely relieved of all symptoms in twenty-four hours.

The rationale for this study was based on recent reports of relief of dysphagia and of cardiospasm in nonpregnant individuals by thiamin chloride, and other reports showing that the heartburn occurring in pregnancy is associated with a cardiospasm and usually a low gastric hydrochloric acid.

After the two hospital patients were relieved of their heartburn, a gastric analysis was done to determine the amount of free acid and combined acid. Both patients were given Ewald test meals, then fractional aspirations, at thirty- and sixty-minute intervals, were taken.

In the patient who was hospitalized for pyelitis and on sulfathiazole therapy the gastric content analysis was as follows:

30 minute test	7.6 per cent free acid
	<u>11.7 per cent combined acid</u>
	19.3 per cent total acids
60 minute test	20 per cent free acid
	<u>25 per cent combined acid</u>
	45 per cent total acids

The patient who was hospitalized for nausea, vomiting, and heartburn had the following analysis:

30 minute test	8.0 per cent acid
	<u>8.7 per cent combined acid</u>
	16.7 per cent total acids
60 minute test	17.5 per cent free acid
	<u>24.8 per cent combined acid</u>
	42.3 per cent total acids

Each patient was then given 300 mg. of nicotinic acid a day, orally, along with the thiamin, plus 6 mg. riboflavin. Fractional analyses were done again after three days with the following results. The pyelitis patient had:

30 minute test	17 per cent free acid
	<u>18 per cent combined acid</u>
	35 per cent total acids
60 minute test	49 per cent free acid
	<u>24 per cent combined acid</u>
	73 per cent total acids

The patient who had nausea and vomiting had:

30 minute test	14 per cent free acid
	<u>21 per cent combined acid</u>
	35 per cent free acid
60 minute test	29 per cent free acid
	<u>24 per cent combined acid</u>
	53 per cent total acids

glucose, fell into the hypoglycemic zone (60 mg.). The patient had no reaction at this time.

The blood electrolytes were as follows: the NaCl of 585 mg. was within normal range; as was also the blood potassium at 17 mg. The latter we expected to find elevated. However, the blood Na level, as expected, was 294 mg., i.e., lower than normal. Our normal controls averaged blood sodium levels of 316 mg. by comparison.

An endometrial biopsy was done and although several uterine quadrants were energetically curetted, the pathologic report was "insufficient material for diagnosis." We therefore assumed the presence of an atrophic endometrium. Prolan and estrin were absent in the urine.

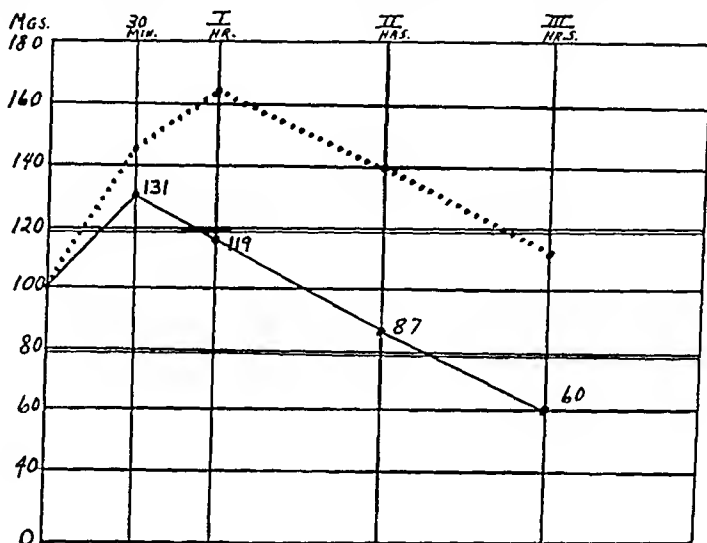


Fig. 1.—Glucose tolerance curves. Hypothetical normal. ——— Patient's curve.

It was deemed inadvisable to subject this patient to the rigors of the salt deprivation test of Cutler, Power and Wilder,² particularly since fatalities reported by Garvin and others³ following its use. However, Robinson, Power, and Kepler⁴ recently reported a modified test that we performed upon this patient with the following results:

In the first part of the test, the night volume of concentrated urine was greater than that voided during any single hour after the administration of the suggested 9 c.c. of water per pound of body weight.

In the second part of the test the factor obtained by their equation:

$$A = \frac{\text{Urea in urine (719 mg. \%)} \times \text{chloride in plasma (590 mg. \%)}}{\text{Urea in plasma (12.5 mg.)} \times \text{chloride in night urine (576 mg. \%)}} \\ \times \frac{\text{Vol. of largest hourly urine (115 c.c.)}}{\text{Vol. of the night urine (300 c.c.)}} \text{ was 22.6.}$$

The patient therefore satisfied their requirements for a presumptive diagnosis of Addison's disease. Their criterion was a factor below 25, nephritis having been ruled out.

X-ray Findings.—The stomach, after a barium meal, was reported to be normal. The sella tureica was also normal. Flat plate of the chest showed a small, central heart as expected⁵ in this disease, and numerous calcified glands in both hili. Flat plate of the abdomen showed flaky

A CASE OF ADDISON'S DISEASE ASSOCIATED WITH PRIMARY AMENORRHEA*

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THIS case seems worthy of presentation because of the many interesting problems encountered in establishing a diagnosis and because of the unusual implications of the associated primary amenorrhea.

History.—The complaints of this 26-year-old patient were those characteristic of the disease; namely, pigmentation of about 2 to 3 years' duration, gastrointestinal symptoms such as nausea, occasional vomiting, and loss of appetite for about the same length of time, accompanied by frequent headaches, frequent colds, and asthenia. She had found it increasingly difficult to carry on her work and household duties because of weakness and fatigue and she had lost about 30 pounds in the past seven years so that she weighed 107 pounds when she first presented herself. She has never menstruated, although the other members of her family were normal in this respect. She has been married for three years, but has had no pregnancies. About three years ago her tonsils were removed to relieve her frequent colds, but without effect; in fact her colds were even more numerous after the tonsillectomy. The family history was negative for tuberculosis.

Physical Examination.—Before therapy, the patient appeared listless, apathetic and somewhat poorly nourished. She seemed to have normal feminine development and sex characteristics. Her skin was generally bronzed and there were deeper spots of pigmentation upon the forehead, upon the face, in the axillae and upon the chest, forearms, and the palmar surface of the hands. The lips presented darkened areas and the gums and hard palate showed a few areas suggestive of "ink spots." There was no vaginal pigmentation.

The hair was soft and silky and was scant in the axillae and over the pubis. The breasts were somewhat small but gave the appearance of having been larger, and this fact was substantiated by the patient. Her span, total height, torso, and leg measurements had the normal ratio. Upon vaginal examination, the clitoris was found to be small and the uterine fundus was also small with a depth of 6 cm. Her blood pressure was 112/98 and remained around 110/86 during her hospital stay. Other findings were not pertinent.

Laboratory Studies.—The urine was entirely negative and the specific gravity was 1.020. The hemoglobin was 84 per cent; red blood count, 4,690,000; white blood count, 7,350. Differential count showed 50 per cent polymorphonuclear leucocytes and 48 per cent lymphocytes. The basal metabolic rate was minus 3 per cent. The routine blood chemistry and the electrocardiogram were normal.

The glucose tolerance curve (Fig. 1) was that characteristically found in untreated Addison's disease¹ in that there seemed to be an increased tolerance. The last two specimens fell below the original fasting level and the final one, taken three hours after the administration of the

*Presented at a meeting of the Clinical Pathological Section of the Cleveland Academy of Medicine, November 7, 1941.

by their receiving inadequate stimulation from the diseased adrenal glands. This disease, in our case, probably began at about the time of puberty.

Treatment.—The patient so far has responded fairly well to the administration of 9 Gm. of sodium chloride daily in enteric coated tablets, along with frequent feedings of a high carbohydrate, high vitamin diet. She has gained weight, has much less frequent headaches, nausea, and respiratory infections. Further, her vigor has increased and she no longer finds it difficult to carry on her work. No doubt at some future time, as her disease progresses, additional therapy along the lines recommended by McGavaek⁵ and Thorn⁸ with desoxycorticosterone in oil or its implantation in pellets or the use of adrenal cortical extract, will have to be resorted to in this patient.

Summary

The history, physical, laboratory, and x-ray findings of a case of Addison's disease with associated primary amenorrhea are presented, along with comments and a probable explanation of her failure to menstruate.

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OVARIAN PREGNANCY ASSOCIATED WITH ENDOMETRIOSIS IN SAME ORGAN*

CHARLES H. MCKENZIE, M.D., F.A.C.S., MINNEAPOLIS, MINN.

THE association of pregnancy with endometriosis of the same ovary is of such unusual occurrence that a report of such a case appears warranted.

Mrs. R. S., housewife, aged 25 years, was admitted to Asbury Hospital on Oct. 30, 1941, and discharged on Nov. 9, 1941. Vaginal bleeding of three weeks' duration brought her for examination, following which she developed sudden sharp pain in the lower right quadrant of the abdomen, shock, bilateral shoulder strap pain, leucocytosis (22,000 white blood cells per c. mm.). The diagnosis was ruptured right ectopic pregnancy.

At operation about 500 c.c. of free blood and 100 c.c. of old clots were removed from the lower abdomen and pelvis. The left ovary contained a follicular cyst 2 cm. in diameter. The cul-de-sac contained nodules typical of endometriosis. The right tube appeared normal and was not

*Presented at a meeting of the Minneapolis Academy of Medicine, March 12, 1942.

calcifications at the upper pole of the right kidney and several calcified flecks in the region of the upper pole of the left kidney. The x-ray diagnosis was calcifications of the adrenal glands.

Discussion

In face of the indisputable x-ray evidence of Addison's disease no other diagnosis could be entertained. The history and the physical findings were typical. A low blood pressure is not essential in order to entertain this diagnosis and may be dependent upon the severity of the disorder. The basal metabolic rate and the blood count are likewise of little diagnostic import, although in this instance the relative lymphocytosis may be significant of the presence of a long-standing tubercular infection.

The electrocardiogram, which in this case was normal, possibly because of the normal blood potassium, might otherwise have had some diagnostic and therapeutic importance. As pointed out by Thomson,⁶ in the presence of a high blood potassium, the normal amplitude of the QRS complex as compared to the T wave may be changed from a ratio of 3:1 to 1.5:1 or even less. This change is most manifest in the second lead. Winkler and others,⁷ experimenting upon dogs, have verified these findings and McGavaek⁵ emphasizes the return of this ratio to normal, along with the return to normal of the cardiothoracic ratio as determined by serial chest x-rays, as one possible criterion of adequate treatment of these patients.

The glucose tolerance curve here was of the type that suggested to Thorn and his associates a possible explanation for hypoglycemic reactions and even death observed in these patients⁸ following the administration of glucose during a crisis. To offset the possibility of this type of reaction he⁸ suggests the frequent or continued administration of glucose or the regulation of glucose oxidation and of gluconeogenesis by the administration of adrenal cortical extract. In this connection McGavaek⁵ illustrates the alteration of the glucose tolerance curve toward the normal by the addition of vitamin B to the diet. Thorn,⁸ however, states that vitamin B has little effect in Addison's disease.

As for the electrolytes, McGavaek⁵ states that sodium and chlorides may both be normal in the blood and in the urine even in the presence of adrenal cortical deficiency and that elevation of the blood potassium is inconstant in cases of Addison's disease.

As regards the amenorrhea we feel that there is adequate evidence in the development of this patient's secondary sex characteristics to assume that she reached adolescence with normally developing pituitary and gonads. The absence of eunuchoidism speaks against the existence of a primary ovarian deficiency, while the absence of both estrin and an excess of prolactin in the urine at this time proves the presence of a pituitary deficiency.

The experimental works of Herrick and Finerty⁹ and of Reese, Koneff and Akimoto¹⁰ and others upon adrenalectomized fowl disclose that degeneration of the basophile cells of the anterior pituitary gland was approximately three times more numerous than in normal fowls of similar age and that there was associated with this a marked decrease in the size of the testes. By inference from this work, the failure of mature development of the gonads in our case is probably due to failure of the basophile cells of the anterior pituitary gland caused secondarily

rupture. This site of rupture was filled with a hematoma containing decidual fragments. The sac contained many chorionic villi.

The corpus luteum is immediately adjacent to the sac containing the chorionic villi, but a definite layer of decidual-like tissue interposes between the sac and the corpus luteum.

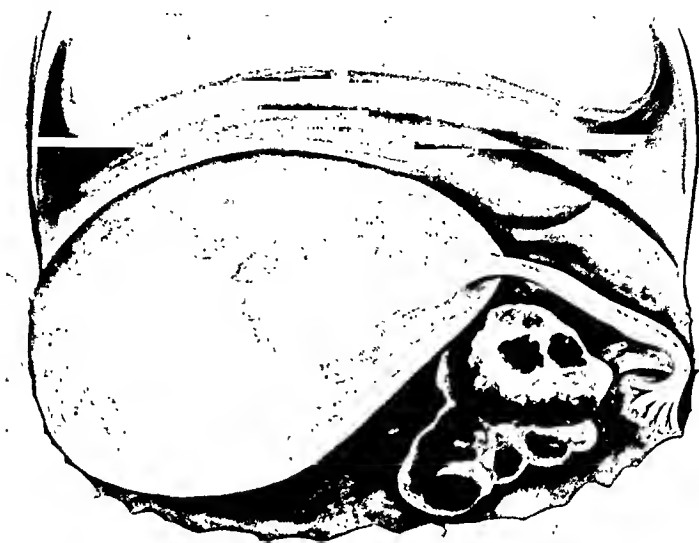


Fig. 4.—Ovarian pregnancy, tube intact.

On the opposite side of the sac the ovarian tissue contained several small cysts. These cysts were lined with typical endometrial gland cells, and the stroma surrounding each cyst showed decidual reaction.

The embryo was not found.

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Bornstein, S., and Israel, M.: Agglutinogens in Fetal Erythrocytes, *Proc. Soc. Exper. Biol. & Med.* 49: 718, 1942.

The red cells of 19 fetuses, varying from 7 to 50 cm. in length, were tested for A, B, M and N agglutinogens. These were found to be present in each instance. Five of these, the smallest being 17 cm. in length, were tested for the Rh factor. Four, including the youngest, were Rh positive.

L. M. HELLMAN

removed. The right ovary contained a corpus luteum of pregnancy in the outer pole. A mass of blood clot extruded from the posteromedial aspect of the ovary. This area was the source of hemorrhage. This ovary was removed.

Pathologic Report.—*Gross:* The right ovary, 3 cm. by 2 cm. by 1½ cm., contained a corpus luteum. At the posteromedial pole a clot of blood extruded from a ruptured sac. *Microscopic:* Section showed the sac to be completely surrounded by ovarian tissue, except at the site of



Fig. 1.—Chorionic villi in sac in ovary.



Fig. 2.



Fig. 3.

Fig. 2.—Ovarian pregnancy shows (1) chorionic villi, (2) decidua reaction of wall of sac, (3) ovarian stroma, (4) endometriosis.

Fig. 3.—Endometrial cyst, endometriosis, in ovarian stroma. Note decidua reaction of endometrial stroma surrounding cyst. High power of "A" in Fig. 2.

AN INTERNAL PELVIMETER FOR APPLICATION DURING AN ABDOMINAL CESAREAN SECTION*

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A ROUTINE procedure in our clinic is the measurement of the obstetric conjugata vera of the pelvic inlet during the performance of abdominal cesarean sections. The pelvimeters on the market have proved to be unsatisfactory for this purpose and stimulated the design of an instrument which has proved satisfactory.

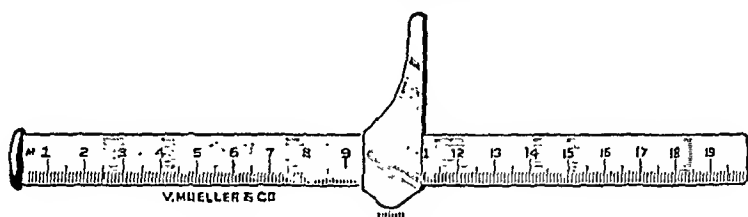


Fig. 1.

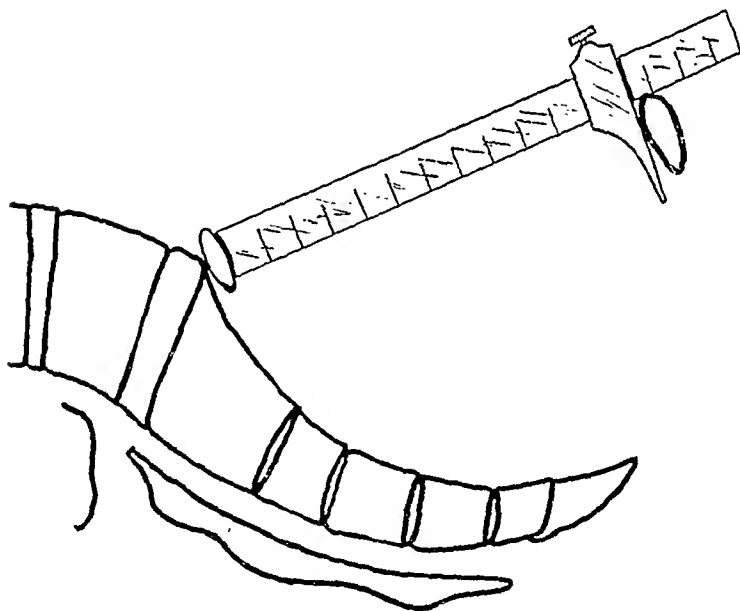


Fig. 2.

The pelvimeter consists of a metal rod knobbed at one end and graduated in millimeters up to 20 cm. A movable metal indicator with a setscrew on its upper extremity is fitted to the metal rod. The indicator after being set to its indicated position is fixed by the setscrew (Fig. 1).

*The instrument was made by V. Mueller & Co., Chicago, Ill.

SYMPATHETIC ANESTHESIA IN LABOR

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(From the Departments of Surgery and of Obstetrics, Johns Hopkins Hospital and University)

IN 1927 Dellepiane and Badino reported the use of unilateral paravertebral block for relief of pain in labor. In an effort to achieve the same end Cleland, in 1933, injected the eleventh and twelfth spinal roots bilaterally. The chance observation by one of us (H. S.) that a patient with bilateral lumbar sympathectomy underwent painless labor, led to a repetition of these experiments.

Seventeen primiparas and 10 multiparas in active labor were used as subjects. The sympathetic blocks were carried out bilaterally, according to the technique of Labat. Injections were made at various levels from the eleventh thoracic to the third lumbar. Several local anesthetic agents were tried, namely one-half per cent procaine, 60 c.c.; one-half per cent procaine, 60 c.c., followed by 3 to 5 c.c. of eucopin in oil; and 1-2000 pontocaine, 60 c.c.

Except in one case, where there was technical failure, prompt relief from pain occurred in every instance. This was of relatively short duration, never exceeding four hours. Deep descent of the head into the pelvis caused a recurrence of pain. In no case did the block appear to influence the course of labor, delivery, or the well-being of the child.

The block itself is not painless, nor altogether without danger. The restlessness of the parturient woman adds to the difficulties and indeed, in one instance, this factor led to the breaking off of a needle. Nevertheless, the fact remains that, for a short time at least, first stage pains can be alleviated by lumbar sympathetic block. With the anesthetic agents now available, the relatively short duration of the block makes this procedure of little clinical value. It is hoped, however, that the present emergency may serve as a stimulus for the development of prolonged acting local anesthetics. Should such prove to be the case, lumbar sympathetic block as a method of relieving pain in labor would seem to merit reinvestigation.

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latter were not listed in detail. MacNalty⁸ in a study of 770 puerperal deaths in England for the year 1934 reported one death due to severe hemorrhage from a gastric ulcer during the puerperium. In a study on Maternal Mortality in New York City, Hooker⁹ reports that from 1930 to 1932 (a three-year period), in 67 representative New York City institutions (comprising 74.7 per cent of all New York City deliveries), there were 348,310 live births. "There was a total of 1,564 puerperal deaths which include all the deaths that occurred during pregnancy and labor." Of these deaths, one resulted from a perforated gastric ulcer. Sandweiss, Saltzstein and Farbman² found only one death due to perforation of a duodenal ulcer among all the 70,310 pregnant women admitted to five Detroit hospitals during a period of ten consecutive years (1928-1937).

Because we encountered a death from duodenal ulcer during pregnancy, we instituted a search of the literature for fatal perforation and hemorrhage from peptic ulcer during pregnancy and puerperium. We found 13 cases of women who have died as a result of these complications. The diagnosis was confirmed by autopsy. Six additional deaths were reported to have been due to these ulcer complications, but no autopsies were performed.

As stated above, of 70,310 pregnant women admitted to five Detroit hospitals during a ten-year period (1928 to 1937), one proved case of peptic ulcer was recorded.

Case Report

The following is a report of the case as obtained through the hospital records:

Mrs. F. B., white, aged 42 years, para x, was admitted to the Herman Keifer Hospital, Aug. 16, 1931, in the sixth month of pregnancy.* She gave a history of pain in the right upper and lower quadrants, spasmodic in nature, of four days' duration. The history was obtained from her husband who stated that his wife had been having intermittent heartburn and indigestion for an indefinite but long period of time prior to the present pregnancy. Soda bicarbonate relieved the heartburn and indigestion. All her pregnancies were uneventful except the ninth, which was complicated by eclampsia.

Examination disclosed a well-nourished woman in shock. Pulse was rapid and thready. Extremities were cold and clammy. There was heavy perspiration on face and forehead. Respirations were rapid. Temperature was 98° F. Heart rate at apex was 160. There was no enlargement and no murmurs. Entire abdomen was markedly tender, patient crying out with pain when touched. There was rigidity in the right upper rectus where tenderness was most marked. The uterus was tense and contracted. There was no external bleeding. On rectal examination, the cervix admitted one finger. The presentation was cephalic. Blood pressure 112/98.

Provisional Diagnosis.—(1) Cystic duct stone, and (2) threatened abortion.

Treatment for shock was instituted. On the next morning, Aug. 17, 1931, the patient suddenly began to scream with pain in the epigastrium

*We express our appreciation to Dr. Ward F. Seeley for permission to report this case.

Our procedure is as follows: After the child is delivered, and before or after the hysterotomy incision is sutured, the obstetric conjugata vera is measured. The uterus is displaced laterally, the knobbed end of the metal rod is placed against the promontory of the sacrum and the lower end of the metal rod is placed against the superior border of the symphysis pubis. The indicator is moved to rest against the posterior surface of the symphysis pubis and is fixed by the setserew. Then the instrument is removed and the measurement of the obstetric conjugata vera is determined when the operation is completed (Fig. 2).

55 EAST WASHINGTON STREET

DEATHS FROM PERFORATION AND HEMORRHAGE OF GASTRODUODENAL ULCER DURING PREGNANCY AND PUERPERIUM

A Review of the Literature and a Report of One Case

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ACTIVITY of peptic ulcer during pregnancy is rare. Ulcer complications, such as perforation or hemorrhage, are even more rare. Early recognition of these complications is important so that adequate therapy may be promptly instituted.

In previous communications,^{1, 2} we called attention to the rarity of active peptic ulcer and its complications during pregnancy, and the apparent beneficial influence of pregnancy on the symptoms and course of peptic ulcer.

Reports in the literature show that a peptic ulcer may become active during pregnancy. Szenes,³ while reporting instances indicating that pregnancy exercises a beneficial effect on the symptoms and course of peptic ulcer, presents brief case histories of seven pregnant women who experienced ulcer distress during their pregnancies. On one of them a gastroenterostomy was performed during the second month of gestation without ill effect. Mussey⁴ of the Mayo Clinic reported 370 operations of necessity during pregnancy over a period of ten years. Two of these were for peptic ulcer. Sandweiss, Saltzstein, and Farberman² interviewed 46 women with proved duodenal ulcers. Twenty-five of these women had 52 pregnancies during the life history of their ulcers. One experienced ulcer symptoms during one of her pregnancies. Vignes⁵ states that pregnancy may at times aggravate the symptoms of ulcer.

Perforation and hemorrhage from gastroduodenal ulcer during pregnancy and the puerperium, and death resulting therefrom, are almost unheard of. Fellner⁶ states that not a single case of ulcer perforation was recorded in 38,000 births. Grace Abbott⁷ of the United States Department of Labor, Children's Bureau, in a study on Maternal Mortality in fifteen states, reported that during the period from February, 1927, to July 1, 1929, there were 1,176,603 live births and 7,380 puerperal deaths. Of these deaths, four were due to intestinal obstruction and ten were due to some other diseases of the digestive system. The

taken care of her since childhood and he had never seen or obtained a history of any gastric or intestinal disorder." In the third case, "Outside of the ordinary slight stomach complaints of the indefinite type, the patient was really never ill." The fourth case "complained of hyperacidity as a chronic disease from before pregnancy and the patient said that the symptoms became better at every pregnant time."

6. Six of the patients (during their last pregnancy) had signs and symptoms of renal pathology: 3 had persistent albuminuria and 3 had edema, 1 of the 6 had "forty convulsions." Another of the 6 patients had a tuberculous kidney and still another, a cystic kidney.

Of interest in this group is a case of Dr. Rae T. LaVake²⁵ of Minneapolis (heretofore not published but merely referred to by Adair and Steiglitz¹⁹ as "the only death reported in the material of the Department of Pathology, of the Minnesota General Hospital"). Dr. LaVake kindly forwarded us a detailed history of his case, in which he indicates that the epigastric pain experienced by the patient prior to death was interpreted as a manifestation of pre-eclamptic toxemia. The autopsy showed a perforated duodenal ulcer with general peritonitis.

7. Four of the mothers had, at autopsy, evidence of tuberculosis: two had tuberculosis of the lungs; one had subacute miliary tuberculosis of the peritoneum and the fourth, tuberculosis of the kidney.

8. All of the patients died (from perforation or hemorrhage) from ten hours post partum to twenty-three days post partum.

9. Prior to autopsy, death was thought to be due to the following: (a) *Hemorrhage cases*: varicosities from esophagus, gastric malignancy, "cardiac death," nephritis. (b) *Perforation cases*: Mesenteric thrombosis, twisted cystoma, acute pancreatitis, cystic duct stone, ruptured gall bladder, eclampsia, septic peritonitis, puerperal sepsis.

In one case, peptic ulcer as the source of bleeding was considered "but was thought to be very unlikely because of the absence of complaints and the rarity of ulcers during the pregnant state."

Discussion

Pyrosis, vomiting, and epigastric pain during the second and third trimesters of pregnancy in a woman with a history of a pre-existing ulcer should be considered as "warning signals" of ulcer reactivation. Acute epigastric pain, rigidity of the upper abdomen, hematemesis, melena, or collapse warrants the suspicion of perforation or hemorrhage of the ulcer. Epigastric pain during the pre-eclamptic state in a woman having a history of ulcer should be suspected as possibly due to peptic ulcer.

Unfortunately, patients admitted to the obstetric or gynecologic services are not as a rule questioned closely with respect to past gastrointestinal symptoms even if distress exists. The history of previous attacks, although difficult to obtain at times, is the most important if not single factor in arriving at a diagnosis of ulcer. While no definite history of ulcer distress was recorded prior to the pregnancy in the above cases, nevertheless most ulcer patients have a "past." The history of previous attacks can be obtained from most patients if an effort is made.

and went into severe shock. The pain, at that time, was localized in the epigastrium and rigidity of the abdomen immediately followed. Treatment for shock was again instituted. The following impressions were noted on the chart: (1) acute pancreatitis, (2) perforated gastric ulcer, (3) ruptured gall bladder.

At 2:15 A.M. of Aug. 19, 1931, patient became comatose and died. At necropsy, a perforated ulcer, approximately 6 mm. in diameter, was found in the anterior wall of the duodenum. There was no obstruction to the flow of bile through the ampulla of Vater.

Analysis of the Cases Previously Reported in the Literature

The first reference in the literature to an autopsy report showing hemorrhage from ulcer as the cause of death during pregnancy was made by LePlay¹⁰ in 1905. LePlay reports a case of a woman, aged 27 years, who during the fourth, fifth, and sixth months of pregnancy had recurrent attacks of severe vomiting, was unable to retain any food, lost considerable weight, became weak and developed a marked degree of anemia. The feces were liquid and dark brown in color. (The report does not state whether the patient had any gastrointestinal distress prior to onset of pregnancy.) During the seventh month, while in the hospital, the patient developed hematemesis, vomiting about a liter and a half of a dark fluid. The vomiting could not be controlled and abortion followed. Hematemesis and melena continued until death ensued. Autopsy showed an extensive ulcer on the lesser curvature of the stomach with serosa forming the base of the ulcer.

Gminder,¹¹ Merckel,¹² Kamann,¹³ Bauereisen,¹⁴ Kuntz,¹⁵ Stephan,¹⁶ Hekscher,¹⁷ Ikeda,¹⁸ Hooker,⁹ Adair and Steiglitz,¹⁹ and Muslow and Brown²⁰ followed, in order named, with reports of deaths from perforation or hemorrhage from ulcer during pregnancy or puerperium with autopsy reports indicating the causes of death. Each author reported one case, with the exception of Kuntz who reported two cases.

Chabannes,²¹ Humpstone,²² Zweifel,²³ Leloirer,²⁴ and MacNalty⁸ each reported a death during pregnancy or puerperium from either perforation or hemorrhage from ulcer, but without proof of autopsy.

An analysis of the 13 deaths (with autopsy reports) brings out the following:

1. Three of the mothers were primiparas; 3 were secundiparas; 2 tertiparas; 1 a para ix; and in 4, the parity was not stated. The ages of the patients ranged between 20 and 41 years.

2. Four of the cases are known to have given birth prematurely: one in the fourth month, two in the seventh, and one in the eighth month. Seven are known to have gone to full term and the remaining two probably went to full term. (There was no definite statement in the reports.) Three of the mothers had twin pregnancies.

3. Seven of the patients had gastric ulcers and 6, duodenal ulcers. Of the 7 patients who had gastric ulcers, 4 died from perforation and three from hemorrhage. Of the 6 patients who had duodenal ulcers, 5 died of perforation, and one of hemorrhage.

4. Nine of the patients died of peritonitis as a result of ulcer perforation and four from hemorrhage.

5. A statement as to past gastrointestinal symptoms (prior to the last pregnancy) appeared in only four of these records. In one, "the past history was essentially negative except for chronic constipation." In another, the family physician advised the consultant that "he had

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PLAUT-VINCENT'S CERVICITIS AND VAGINITIS

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SINCE Plaut (1894) and Vincent (1896) described the fusospirochetal infection commonly associated with Vincent's name alone, there have been an increasing number of reports of this infection in sites other than the mouth. Fusospirochetal infection of the female genital tract is rare, despite the high incidence (58 per cent) of the organisms in the smegma of normal women reported by Pilot and Kanter.^{15, 16} The low incidence of this disease in the female as contrasted with the more frequent occurrence in the male is regarded by Hinman⁴ as evidence against the venereal character of the disease. It is interesting to note that the organisms, though abundant around the vulva, are extremely rare in the vagina, and are found with the utmost rarity in cervical discharge.

To date there have been but 32 cases of genital Plaut-Vincent's disease reported in the female; in these cases there were 16 instances of vulval lesions, 15 of vaginal lesions, and but 5 cervical lesions reported (Table I). The uterus has been reported as the site of infection in 2 cases.

In the 14 cases presented above, the ulcer complications occurred immediately or shortly after the birth of a premature fetus or full-term child. When indications are present, pregnancy or puerperium should not be considered as a contraindication to surgical therapy. Six successful operations were performed without ill effect on mother or fetus at the Mayo Clinic²⁶ and one at the Peham Clinic²⁷ (Woman's Clinic at the University Institute, Vienna). We were unable to find any reports of operation during the puerperium.

Many more than fourteen deaths during pregnancy and puerperium may have occurred as a result of these complications but the deaths are probably classified as "other accidents of pregnancy."

Summary

1. While pregnancy as a rule has a beneficial effect on the symptoms and course of peptic ulcer, active symptoms of ulcer may occur during pregnancy. Nausea, vomiting, and epigastric distress or epigastric pain during the second or third trimester of pregnancy in a woman with a history of a pre-existing ulcer should be considered as "warning signals" of ulcer reactivation. Medical management should be immediately instituted to prevent hemorrhage or perforation of the ulcer. These complications may follow with fatal results, particularly during the first several days of the puerperium.

2. Thirteen deaths, resulting from perforation and hemorrhage from gastroduodenal ulcer during pregnancy and puerperium, with autopsy reports, were found in the literature. We have added one case, the only record of peptic ulcer in all the 70,310 pregnant women admitted to five Detroit hospitals in a period of ten consecutive years. Probably more deaths during pregnancy and the puerperium occurred as a result of ulcer complications but the deaths may have been classified as "other accidents of pregnancy."

3. In the above 14 cases, prior to autopsy, death was thought to be due to varicosities from esophagus, gastric malignancy, "cardiac death," and nephritis in the hemorrhage cases, and mesenteric thrombosis, twisted cystoma, acute pancreatitis, cystic duct stone, ruptured gall bladder, eclampsia, septic peritonitis or puerperal sepsis in the perforation cases.

4. Ulcer patients as a rule have "a past." The typical ulcer history (intermittent attacks, food, soda relief, etc.), while at times difficult to obtain, may be the decisive factor in arriving at a proper diagnosis and in instituting adequate therapy.

5. Pregnancy or puerperium should not be considered as contraindications to surgery when this is indicated for peptic ulcer.

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rigidity or rebound tenderness. There was no inguinal lymphadenopathy. On pelvic examination a nulliparous introitus was found, Skene's ducts and Bartholin's glands were negative, no urethral discharge was noted, and no secretion was obtained from the urethra upon stripping. The cervix was slightly enlarged, firm, and shallow irregularities could be palpated over its surface. There was a bilateral parametritis and manipulation of the cervix was accompanied by exquisite pain.

The uterus was acutely anteverted and of normal size. The adnexa were not palpably enlarged or tender.

Speculum examination showed a thin, purulent, sanguineous discharge having a slightly fetid odor. The cervix was enlarged, reddened, and extensively ulcerated. The ulcerous area was covered with a tenacious dark gray membrane, somewhat diphtheritic in appearance, which had a foul odor. A membrane of similar appearance covered a large area of the adjacent vaginal mucosa and extended over most of the posterior vaginal vault.

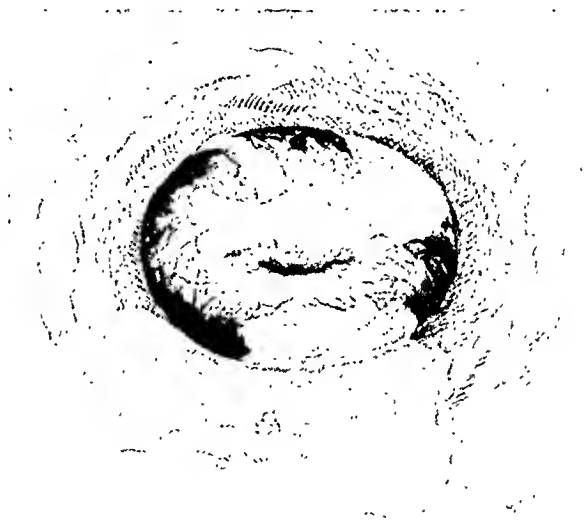


Fig. 1.

Smears and cultures were made from material obtained from these areas and found to be negative for gram-negative diplococci. The smears and dark-field examinations of material obtained from the ulcerated areas were laden with the fusospirochetal organisms of Plaut-Vincent's. The Wassermann and Kahn reactions were negative.

The patient was given morphine, gr. $\frac{1}{4}$, and an effort was made to débride the cervix and vagina of as much of the gray membrane as possible. Considerable bleeding occurred. The vagina and cervix were first scrubbed with green soap and water, followed by application of ether and painting with 2 per cent aqueous gentian violet solution. The vagina was insufflated with sodium perborate powder. For the next three days the patient douched 4 times daily with a solution of 15 Gm. of sodium perborate to 1 liter of water. Each douche was followed by painting of the cervix and vagina with gentian violet and insufflation of the vagina with sodium perborate powder.

TABLE I. REPORTED CASES

AUTHOR	YEAR	NUMBER OF CASES	GENITAL AREAS INVOLVED			
			VULVA	VAGINA	CERVIX	UTERUS
McConnell	1916	1			1	
Werner	1919	1		1		
Philipp	1924	1		1		
McCormac	1925	1	1			
Robinson	1927	1		1		
McIntyre	1928	1		1		1
Pilot	1929	1		1		
Brown and Barlow	1929	1		1		
Roberts	1929	1		1	1	
Arnold	1930	1		1	1	
Lash	1930	1		1		
O'Sullivan	1931	1		1		
Jump and Sperling	1932	1		1		
Mandy	1932	1		1	1	
Goldschmidt and Furstner	1933	2	2			
Muntz	1934	1		1		
Von Haam	1938	14	13	1	1	1
Quindlen and Taubenhaus	1940	1		1	1	
This report	1941	1		1	1	
Total		33	16	16	6	2

In adults having the infection limited to the genital tract, a history occasionally has been obtained of transmission from the organism-laden saliva of the sex partner. This was clearly illustrated in the case reported by McCormac,⁹ whose patient developed an ulcer on the labia minora several days after intercourse with a man who had "sore throat," and used saliva as a lubricant for coitus. A similar history was reported by Quindlen and Taubenhaus¹⁹ and in the present case. In children the introduction into the vagina of objects that have been in the mouth or the introduction of contaminated fingers into the vagina has been reported as the source of infection, as in the cases of Brown and Barlow² and Pilot.¹⁷ Interestingly enough, Von Haam²³ was able to find only one case in his series of 14 in which transfer of infection from the mouth to the vagina could be demonstrated. This was the mode of transmission also in the cases of Arnold,¹ Robinson,²¹ and Roberts.²⁰ McIntyre,¹⁰ Philipp,¹⁸ Lash,⁷ and Von Haam²³ have each reported an instance of puerperal fusospirochetal infection.

Case Report

Mrs. L. K., a 26-year-old white female, was first seen Sept. 12, 1941, at which time she complained of extreme pain in her lower abdomen and pelvis; pain had become increasingly severe since its sudden onset early in the morning three days previously. She had been married for three months, her menstrual periods were regular and her menstrual history (13 × 28 × 4) was normal. Her last period occurred twelve days previously and was uneventful.

Physical examination revealed a well-developed, poorly nourished, asthenic white female, who appeared to be in considerable pain. Temperature was 99.8° F., pulse 100, and blood pressure 110/80. The examination of the head, neck, thorax, and extremities revealed nothing pertinent to this report. The abdomen was scaphoid and exquisitely tender throughout. The tenderness was slightly more marked just above the symphysis and in the lower left quadrant. There was no

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300 MEDICAL ARTS BUILDING

THE HISTIDINE TEST (KAPELLER-ADLER) IN THE DIAGNOSIS OF PREGNANCY

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NOTWITHSTANDING the proved adequacy of the Aschheim-Zondek test in the determination of pregnancy, efforts have been made in the past few years to devise other tests which might prove more economical, more rapid, and equally reliable. Some of the more recent tests used are the colostrum skin test,¹ which is based on an allergic skin reaction; the South African frog test (*Xenopus laevis*),² which is based on the injection of pregnancy urine into the lymph sac of the frog, producing a deposit of ova within six to eight hours; the six-hour immature rat test³ in which a macroscopic change is produced in the ovary by a subcutaneous injection of pregnancy urine.

A recent perusal of the medical literature, particularly the Scandinavian⁴ and Continental,⁵ reveals an increasing utilization of a chemical test devised in 1933 by Kapeller-Adler⁶ for the rapid determination of pregnancy. This test is based on the detection of histidine in the urine

On September 16, four days after the first treatment, marked improvement was noted. The abdominal pain had completely subsided and the pain produced by manipulation of the cervix decreased. While there was no change in the size of the areas of involvement, no new membrane formation was noted. Treatment with gentian violet and sodium perborate was continued for an additional three days and then, following the suggestion of Quindlen and Taubenhaus,¹⁹ the involved areas were swabbed daily with a solution of 2 per cent arsphenamine in glycerin. The patient slowly improved and within five weeks, after first being seen, the vagina and cervix were completely healed. She was examined three times subsequently at intervals of one month; there was no recurrence.

Comment

In view of the wide occurrence of oral fusospirochetal infection and the high incidence of the organisms in the smegma of normal women, it is rather surprising that so few cases of genital fusospirochetal infection have been reported. This is the more striking when one becomes aware of the frequency of the use of saliva as a lubricant in coitus among patients of the clinic class. Smith expressed the opinion that fusospirochetal disease represented "probably quite a common infection especially among the lower classes."²² It is possible that some mild cases are overlooked and cured by the usual hygienic measures prescribed in the general treatment of cervicitis and vaginitis. However, there are undoubtedly many unknown factors which must govern the pathogenic activity of these organisms in the genital tract, as suggested by observations on the high incidence of fusospirochetosis in the vagina of rats deprived of vitamin A.⁵

In contrast to the relatively shallow ulcers, and superficial infections with necrotizing membranous vaginitis which, on smears, shows few organisms and many pus cells, noted in this case and in the majority of reports, Von Haam²³ and Lafferty²⁴ have described a series of cases in both male and female where the pathologic process was extensive, being true Vincent's ulcers and characterized by "necrosis of the infected part with liquefaction; by inflammatory edema with the production of serous exudate and by an abundant amount of organisms." These excellent reports adequately describing the pathology of the condition, the methods of diagnosis, and a large number of cases they observed should serve to focus attention upon this lesion, and upon the necessity of a more careful observation and differential diagnosis of vulvovaginal lesions. In Von Haam's series, only one patient had an associated vaginitis; the other 13 patients had lesions restricted to the vulva.

While the therapy used in the case herein reported was successful, it is not advocated in its entirety. The scrubbing of the vagina with green soap and water, with the subsequent application of ether, is probably too harsh a procedure and need not be used. In general, regardless of the particular therapy used, one should observe these principles: (1) thorough removal of the grayish membrane when present; (2) use of gentian violet and some types of oxidizing agent, e.g., hydrogen peroxide, sodium perborate, or potassium permanganate, during the acute state; (3) application of arsphenamine in glycerin after the subsidence of the acute state or the use of some arsenical preparation locally or intravenously. It is interesting to note that the patient in the case reported by Quindlen and Taubenhaus¹⁹ had received intravenous arsenical therapy with no apparent value.

One cubic centimeter of the ammoniacal solution* is now layered on the urine and the test tube heated in a boiling water bath for two or three minutes. If histidine is present, a reddish-violet colored ring appears. The color may develop within a very short time and gradually spread throughout the urine. If no histidine is present, a brownish precipitate is usually seen.

Results

The urines of 56 pregnant women were tested. The cases were obtained from the ward service, the prenatal clinic, and private patients. Forty-one were primiparas. The tests were done in all months of pregnancy. Fifty-one urines gave a positive reaction and 5 were negative, an accuracy of 91 per cent. Three of the errors occurred in the first trimester of pregnancy, 1 in the second trimester, and 1 in the third.

Eleven of these specimens were also tested by means of the Friedman hormone test. There was agreement in 9 instances. One patient, pregnant five weeks, had a negative Friedman test and a negative Kapeller-Adler test (Case 30). Case 81, seven weeks pregnant, had a positive Friedman test and a negative Kapeller-Adler test. Unfortunately, we were unable to obtain a follow-up on this patient to establish definitely the existence of a pregnancy. Nevertheless, we included this among our errors. Another patient, pregnant fourteen weeks, had a positive Kapeller-Adler test and two negative Friedman tests done one week apart (Case 6). Case 118 was under observation as a suspected ectopic. The Kapeller-Adler test was positive and confirmed at operation.

The urines of 72 nonpregnant women of childbearing age were tested. There were 5 errors. These included patients with various gynecologic disturbances, such as amenorrhea, pelvic infection, fibroids, ovarian cysts, etc. It also included patients on other services in the hospital. Both cases of primary amenorrhea gave a positive reaction. Two of the urines of patients with secondary amenorrhea also gave a positive reaction. Case 103, a patient admitted with an acute head injury, gave a positive test.

The urines of 26 climacteric patients were tested. There were no errors. The urines of 6 males were also tested and all gave a negative reaction. The combined totals constitute a control group of 104 cases. There were 5 errors, giving an accuracy of 95 per cent.

Comment

The results obtained are encouraging enough to warrant further investigation of the Kapeller-Adler test as a rapid method in the diagnosis of pregnancy. A definite relationship between histidine metabolism and pregnancy apparently exists. This relationship opens a fertile field for future study.

NOTE: Kapeller-Adler in her most recent article²⁰ describes the technique of her test as follows:

1. 5 c.c. of urine instead of 10 c.c.
2. Potassium permanganate and sulfuric acid added only to alkaline urines instead of all tested urines.

*Ammonium carbonate, 10 Gm. of ammonium carbonate, 90 c.c. of water, 200 c.c. of pure liquid ammonia.

of pregnant women which was first noted by Voge⁷ and determined by a chemical color reaction first described by Knoop.⁸

In 1935 Seidman⁹ modified the Kapeller-Adler test and reported a study of 102 pregnant and 97 nonpregnant women. There were 94 positive and 8 negative tests in the pregnant group. In the nonpregnant group, there were 24 positive and 73 negative tests, a percentage of 25 per cent false reactions.

The unmodified Kapeller-Adler test gave better results than those reported by Seidman. Stern¹⁰ found that the presence of nitrites in the urine interfered with the detection of histidine. In 1936 Kapeller-Adler¹¹ then altered the technique of the test by oxidizing the nitrites with 1 per cent potassium permanganate after acidulating the urine with 10 per cent sulfuric acid. By so doing, the false reactions were reduced to less than 4 per cent. The reliability of this improved technique has been substantiated by Westberg,¹² and Neuweiler and Grimm,¹³ who claim an accuracy of 99.3 per cent.

The American literature¹⁴ in the past decade contains little reference to this test although some early workers considered it worthy of recognition. Recently, because of difficulty in obtaining laboratory animals, we decided to revive the Kapeller-Adler test.

Normally, histidine, a product of protein metabolism, is disintegrated in the liver by a specific ferment, histidinase.¹⁵ In pregnancy this action is inhibited.¹⁶ The free histidine is then excreted by the kidney without alteration and can then be detected chemically, the rate of excretion being dependent upon the amount of food ingested.¹⁷ Histidinuria appears as early as the first week after the missed menstrual period, and occasionally even before. It disappears a few days after delivery. Kapeller-Adler suggests that the inhibition of the histidinase may be related to the associated rise in prolactin during pregnancy.¹⁸

Technique¹⁹

Ten cubic centimeters of the first morning specimen of urine are acidified with 4 drops of 10 per cent sulfuric acid and oxidized in a test tube by adding 1 per cent potassium permanganate solution, drop by drop, until a fairly reddish color results. This reddish or violet color should stay for about half a minute. If it does not disappear, or if it shows a brown precipitation of manganese peroxide, the test tube should be placed in a boiling water bath. The urine will then become clear in a short time. This oxidation removes the nitrites. If the urine remains cloudy, it should be filtered.

To the clear urine, the bromine reagent* is added, drop by drop, until the solution becomes lemon yellow in color. Then test with potassium iodide starch-paper. One drop of the solution will produce a blue color on the paper if free bromine is present. Care should be exercised not to add too great an excess of bromine as an excess of bromine inhibits the color reaction and is attributed to the interaction of bromine and histidine. After five minutes repeat the test for free bromine. If the paper stains faintly violet, continue with the test. If not, more bromine reagent must be added and tested again by the potassium-iodide starch paper after five minutes.

*Bromine reagent, 1 c.c. of pure bromine, 33 c.c. of glacial acetic acid, 100 c.c. of distilled water.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A TEN-YEAR ANALYSIS OF PUERPERAL SEPSIS DEATHS IN PHILADELPHIA*

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DURING the past ten years the circumstances of every maternal death in Philadelphia have been reviewed by the Committee on Maternal Welfare of the County Medical Society. An attempt is made to determine the primary cause of death in each instance and to classify it as preventable or nonpreventable, ascribing so far as possible the responsibility to the physician or the patient. The 308 case records of this committee listed under "puerperal septicemia" form the basis of this study.

During these years there have been 318,103 total births and 1,790 maternal deaths; 23 per cent were due to septic abortions, 17.2 per cent to puerperal sepsis, 11.1 per cent to toxemias, and 9.0 per cent to hemorrhage of pregnancy. It has been emphasized that nearly one-fourth (23 per cent) of these "maternal deaths" followed septic abortions, a problem unrelated to "maternity" for which the profession is not directly responsible. Of the 413 deaths from septic abortions studied by the Committee, 77.2 per cent were the direct responsibility of the patient who induced or suffered induction of abortion, while only 11.2 per cent were attributed to the physician. During this period the maternal death rate has dropped encouragingly. Although there has been a real decrease in deaths from infection and hemorrhage, greater progress has been made in reducing those from toxemia. This is probably the result of better prenatal care. It is our hope that study of these deaths from sepsis, giving particular attention to the errors of judgment and technique involved, will help reduce them further, since the present total equals that due to hemorrhage and toxemia combined.

Age.—Ages ranged from 15 to 45 years, the median age being 30. The highest death rate occurred in the age group 35 to 39. Septic deaths, like all maternal deaths, are least in the age group 20 to 24.

Race.—Of the 308 women who died of puerperal sepsis 235 were white, 73 were colored. This death ratio of 3.2 to 1 compares unfavorably to the total birth ratio of 5.3 to 1. Only 15 per cent of the total births were in colored women, yet 23 per cent of the septic deaths were in that race. Proportionately twice as many colored women died from reasons ascribable to their own ignorance. The need for increased educational facilities and better obstetric care for the colored patient is obvious.

Parity.—Comprising about 35 per cent of all deliveries, 49 per cent of women dying from post-partum infection were primiparas. There is a steady decrease in deaths in succeeding pregnancies, relatively less with increasing multiparity.

*Presented at a meeting of the Obstetrical Society of Philadelphia, May 7, 1942.

3. Following brominization all traces of free bromide should have disappeared at the end of the five-minute period before the continuance of the test.
4. The ammoniacal solution is mixed with the brominated urine instead of layered and placed in a boiling water bath for three minutes.

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1882 GRAND CONCOURSE
2344 DAVIDSON AVENUE

Schauffler, Goodrich C.: *Pelvic Peritonitis in Female Infants and Children*, Surg., Gynec. & Obst. 71: 286, 1940.

Data from the records of 371 instances of female genital pathology in children and infants have been sifted for material in relation to primary pelvic infection. In 259 cases the original condition centered about a frank vaginal infection, the majority gonorrheal.

By far the most frequent route is thought to be by ascent from an infected vaginal tract. The gonococcus and the pneumococcus, the organisms most frequently involved, invade almost always in this manner. Secondary infection from the appendix is not infrequent, and is always serious.

The pathology is essentially that of pelvic peritonitis.

Appendix infections and pyelocystitis are the most frequent confusing factors.

Pertinent data from personal observations of actual or highly suggestive primary pelvic infection are reviewed.

WILLIAM C. HENSKE

d. Unrecognized transverse lie	1	
e. Unrecognized disproportion	14	
f. Unrecognized placenta previa	1	
3. Meddlesome interference		16
4. Inadequate treatment		13
a. Of toxemia	2	
b. Of second stage	5	
c. Of infection	5	
d. Of inertia	1	
5. Operative interference in the home		10
6. Indefinable error of judgment and technique		6
7. Manipulation in the presence of infection		4
8. Unnecessary cesarean section		3
9. Failure to intervene when indicated		2

Summary

1. Three hundred and eight women died of puerperal sepsis in Philadelphia during the past ten years.

2. Three-fourths of the deaths from puerperal sepsis were deemed preventable.

3. The prevention of puerperal sepsis is chiefly the responsibility of the physician.

4. Puerperal sepsis is greatest in the nullipara, the colored race, and the woman aged 35 to 40 years.

5. Operative interference preceded infection in 57.7 per cent of these patients.

6. Cesarean section was performed on one-third of the patients who died of puerperal sepsis.

7. Obstetric complications cannot be properly treated in the home.

8. The causes of puerperal sepsis vary from violations of elementary principles, through fine errors of judgment and technique, to unavoidable disaster.

Attendant.—A practicing physician attended 214, or 69.4 per cent, of the women dying from puerperal sepsis. The remainder were attended by internes (47, or 15.2 per cent), residents (13, or 14.1 per cent), students (13, or 0.9 per cent), and unknown, 27, or 8.7 per cent. Four women were undelivered.

Method of Delivery.—Spontaneous delivery preceded sepsis in 40.2 per cent of the group; operative in 57.2 per cent. The method of delivery was unrecorded in two instances and four patients died of infection undelivered; 33.1 per cent of these deaths followed cesarean section.

Place of Delivery.—Fatal infections followed delivery in the hospital in 246 instances, in the home in 58. Four patients died undelivered in the hospital. The septic death rate per 1,000 total births for hospital delivery is 1.0, for home delivery 1.15. This does not mean that the danger of infection is only slightly greater in the home than in the hospital, for the latter must bear the burden of delayed admissions, severe toxie and hemorrhagic cases requiring heroic measures, and other complications. Operative interference in the home adds greatly to the danger, increasing the death rate twenty times over the hospital death rate for operative delivery.

Preparation.—Of the 308 patients who died of sepsis, 68 were not shaved before delivery. Fourteen of these deaths were nonpreventable and 16 were caused by neglect on the part of the patient. In 38 cases the physician was in error, and of these, 20 had no preparation whatsoever. Economic factors were largely responsible for this error.

Vaginal Examination.—Nearly one-half of the patients had vaginal examinations during labor, averaging two examinations per patient. It is our belief that many more were unrecorded. This does not condemn vaginal examination per se, but only vaginal examination without proper technique.

Preventability.—Death was considered by the Committee as preventable in 230 instances, and nonpreventable in 78. In the preventable group, the error was attributed to the physician in 206 cases, to the patient in 24. The preventable factor was considered an error in technique in 110 cases, error of judgment in 91, both errors in 3, and unrecorded in 2.

From the above data furnished by the Committee we have been able by inference to list the involved errors of technique and judgment. Some overlapping is unavoidable.

A. Errors in Technique

1. Indefinable error in technique	40
2. Technical error in cesarean sections	29
3. Long labor (probable infection) plus cesarean section	12
4. Home operations, inadequate preparation	8
5. Vaginal manipulation with inadequate preparation	6
6. Sepsis following surgical induction	6
7. Invasion of infected uterus	3
8. Post-partum douches	2
9. Inadequate treatment of hemorrhage and/or infection	2
10. Streptococic throat infection plus cesarean section	1
11. Streptococic infection carried by nurse	1

B. Errors in Judgment

1. Cesarean section in presence of infection	19
2. Error in diagnosis	21
a. Unrecognized ruptured uterus	2
b. Unrecognized hydrocephalus	2
c. Unrecognized placenta accreta	1

for extensive summaries of the early investigations of the potency and toxicity of diethylstilbestrol.

The profession has welcomed certain advantages of diethylstilbestrol over the hormonal estrogens: (1) it is inexpensive; and (2) moderately small amounts by mouth induce estrogenic effects which are comparable to those obtained with the usual therapeutic doses of intramuscularly administered hormonal estrogens. These features may prove to be therapeutic boomerangs unless constant diligence be exercised to avoid meretricious therapeutics, self-medication, overdosage and unduly prolonged treatment.

The most common routes of administration of estrogens are the oral and intramuscular ones. In addition, estrogens have been applied locally to the vaginal and nasal mucosae and by dermal injection when it was desirable to obtain localized effects and to keep general systemic effects at a minimum. Subfascial implantation of sterile pellets of crystalline estrogens has been done.

The convenience of the pellet method is obvious, if and when prolonged therapy is necessary. However, its effectiveness has been questioned on the basis of an unsatisfactory absorption rate.⁴ Moreover, there are other grounds for opposing this method of administration. Since its most common uses have been in the treatment of symptoms sequential to menopause, genesis and growth of neoplasms may be favored by a constant supply of estrogens in amounts greater than the usual physiologic levels. The warning that this form of therapy is contraindicated in women with intact uteri⁵ should be heeded. The cheapness and effectiveness of oral therapy with diethylstilbestrol or estrone sulfate render pellet implantations of estrogens unnecessary even when prolonged therapy is deemed advisable.

More recently, intramuscular administration of an aqueous suspension of estrone crystals has yielded promising results.⁶ Estradiol dissolved in propylene glycol has been applied topically under the tongue with resultant satisfactory absorption.⁷

Substitutional and Complementary Therapy in Intrinsic Estrogenic Failure: Hypo-ovarianism originating during adolescent years rarely impairs health, but it results commonly in ultimate sterility and it imposes upon the young woman various cosmetic inelegances. The sterility which results from severe estrogenic failure of intrinsic ovarian origin is permanent unless spontaneous recoveries of ovarian reactivity occur. Full substitutional therapy with estrogens may effect desired cosmetic alterations, the rationale of which are: (1) to effect epiphyseal closures, thereby curbing excessive somatic growth (a therapeutic hope); (2) to induce sexual attractiveness of the patient with sequential salutary psychic effects; and (3) to produce a degree of genital development comparable to the normal.

A differential diagnosis should be made between estrogenic failure secondary to hypopituitarism or hypothyroidism and that due to intrinsic ovarian inadequacy. Often a trial of gonadotropic therapy (see gonadotropins) may be necessary to segregate those cases due to hypogonadotropic pituitary function. Only when ovarian failure is due to extraovarian causes, can complete therapeutic salvage, i.e., initiation of fertile cycles, be anticipated.

When there is recourse to substitutional estrogenic therapy in severe intrinsic ovarian failure, the limitations inherent in this form of treatment should be recognized: (1) no stimulative effects on the ovaries

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

ENDOCRINE THERAPY IN GYNECOLOGY AND OBSTETRICS

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OUR conceptions of the roles of the endocrine glands in gynecic physiology and functional pathology continue to expand. As a result, we find most widespread, if not always most critical, therapeutic applications of endocrinology in gynecologic and obstetric practice.

The various hormonal agents used in gynecology and obstetrics may be grouped into two general categories: (1) crystalline steroids which comprise hormones of the gonads and adrenal cortex or their derivatives and certain nonhormonal synthetic chemicals with endocrinelike properties; (2) extracts of protein or proteinlike nature derived from the pituitary and thyroid glands and from certain body fluids.

I. The Steroids

The hormonal steroids are related to each other by a common phenanthrene-cyclopentane, or cholane, nucleus, which probably indicates the same chemical precursor. Many investigators believe this to be cholesterol. There are four groups of steroid hormones: estrogens, androgens, progestational steroids, and adrenal cortical steroids.

1. *Estrogens*.—Estrogens are concerned with sexual maturation and the subsequent maintenance of functional adequacy of the sexual system of the female.

There are two groups of estrogens: (1) the hormonal steroids which are derived, in the female, ultimately from the ovaries or chorioplacental system, and (2) the nonhormonal steroids, e.g., diethylstilbestrol and its compounds, which are the handiwork of the synthetic chemists.

There are three hormonal estrogens which are employed in therapy: These are *estradiol* and *estrone*, which usually are administered intramuscularly in oil, and *estriol* which is employed orally either as the free steroid or as its glucuronide. *Estrone sulfate*, a chemical compound recently available commercially, is said to have approximately the potency of diethylstilbestrol when used orally.

The best known of the nonhormonal estrogens is *diethylstilbestrol*. Its synthesis was announced in England in 1938,¹ and it was released into commerce in Europe and Canada in 1939. Diethylstilbestrol was subjected to a thorough investigation by the Food and Drug Administration before its release into commerce in the United States in the early fall of 1941. In June, 1942, it was accepted for inclusion in New and Non-Official Remedies by the Council on Chemistry and Pharmacy of the American Medical Association.² Readers are referred elsewhere³

A satisfactory and conservative means of regulating prolonged and excessive anovulatory bleeding of the young woman employs the ovarian principles, estrogens and progesterone, in a cyclic fashion which simulates their order of production and use by the individual.⁸ An estrogen (estradiol benzoate, 0.3 mg. daily or 0.6 mg. every other day) is given for ten to fourteen days, and subsequently there follows the administration of estrogen (estrone, 10,000 I.U. daily or 20,000 I.U. every other day) and progesterone (or progestin, 5 mg. daily or 10 mg. every other day) for the next ten to fourteen days. Treatments are given intramuscularly and are initiated at the conclusion of an episode of bleeding. As a rule, bleeding occurs near or at the completion of such a schedule.⁹ This system has been modified¹⁰ by various workers to the extent of decreasing the total dosage of progesterone, either by decreasing the daily dose or by decreasing the number of treatments. These series of therapy are continued until bleeding occurs from progestational endometrium, verified by studies of endometrial biopsies.

When immediate hemostasis is desired, satisfactory results usually are obtained by the use of daily intramuscular injections of estradiol benzoate, 0.3 mg. to 1.0 mg. or by the oral administration daily of 3 to 10 mg. of diethylstilbestrol, provided a diagnostic curettage is not indicated and the hemopoietic system is not under strain. If hemostasis is secured by estrogenic therapy, cyclic estrogen-progesterone therapy should follow promptly in order to bring about regulation of the bleeding cycle.

The principal objections to cyclic estrogen-progesterone therapy are its expense and the necessity of intramuscular administration. With diethylstilbestrol available, however, a part of the difficulty may be overcome. It has been employed^{9, 11} in cyclic manner with anhydrohydroxy-progesterone with promising results in the treatment of excessive uterine bleeding. When used in daily doses of 1 to 3 mg., diethylstilbestrol compares favorably with estradiol in regulating uterine bleeding or in "priming" hypoplastic uteri.¹²

Not only does this therapy regulate prolonged or excessive bleeding but also in some 30 to 40 per cent of instances it permits recovery of normal ovarian functions. It possesses, however, little more than emmenagogue value when it is used in estrogenic failure characterized by amenorrhea.

When ovarian failure is due to hypothyroidism, adequate thyroid therapy (q.v.) produces desirable effects upon the bleeding cycle and upon the ovulatory functions of the ovary. If there be need for immediate hemostasis and cycle regulation, estrogenic therapy may be a valuable adjuvant. When sterility exists in association with cyclic anovulatory bleeding, and when there is no associated hypothyroidism, cyclic one-two gonadotropic therapy should be tried (q.v.). This therapy is of no value in regulating bleeding.

Palliative Therapy During the Climacteric: Women who are approaching, or who have experienced recently, a spontaneous menopause and those who have had the menopause imposed upon them through the effects of surgery, roentgen rays or radium, have as complex a series of endocrine adjustments to establish as can be identified with any of the physiologic epochs of woman. In handling the climacteric patient, it is not ovarian failure, per se, which requires therapy; it is the undesired symptomatology which is associated with this epoch.

The therapeutic agent of choice in the treatment of climacteric symptomatology is an estrogen.⁸ Preferably, it should be one which is active

are produced; (2) therapy must be given as long as results are desired; (3) when therapy is discontinued, all the salutary responses regress; and (4) despite striking endocrine responses of patients treated in this manner, they remain sterile, since there are no substitutes for ova produced by healthy ovaries.

The most practical and economic estrogens for prolonged therapy of this type of ovarian failure are diethylstilbestrol and estrone sulfate. These permit oral therapy. The usual daily dosage of diethylstilbestrol ranges from 3 to 6 mg., that of estrone sulfate, probably from 7.5 to 15 mg. When estradiol benzoate or dipropionate is employed intramuscularly, a dosage ranging from 6,000 to 15,000 rat units about three times weekly is required. There are good grounds for advising that estrogenic therapy be given in cycles with some twenty days of treatment and some ten days of no treatment. This regime simulates natural waves of ovarian function and prevents cumulative effects of prolonged constant therapy. When sufficient uterine hypoplasia has occurred to permit withdrawal bleeding, these cycles of therapy should be initiated after withdrawal bleeding and discontinued if and when intercurrent bleeding occurs. Commonly, diethylstilbestrol therapy under these circumstances produces almost ebony black pigmentation of the nipples and areolae: this has been found to be of no significant import, and it has been likened to the hyperpigmentary reactions of the gestational state. The concomitant administration of progesterone or anhydro-hydroxy-progesterone with estrogens is said to lessen regressions which follow cessation of therapy. This additional therapy increases the cost of the therapeutic program many times.

When hypomastia is the only cosmetic concern of the patient, some clinicians advise the use of an estrogenic ointment, containing either estradiol or diethylstilbestrol. The ointment is massaged into the mammary areas several times daily. This method of therapy is more troublesome and more expensive than the oral one.

Anovulatory ovarian failure during adolescence, which is characterized by no evidences of estrogenic deficiencies, is common during the early post-menarcheal months. At times, it may continue for longer periods of time, when it may be associated with prolonged and excessive uterine bleeding. Since the gynecologist is charged under these circumstances with the securing of hemostasis and the regulation of bleeding without producing any further depressions in ovarian function and since he desires ultimately for his patients to recover a grade of ovarian function compatible with fertility, the most conservative therapeutic approaches must be employed. This therapy is discussed in the coming sections which deal with anovulatory failure during the reproductive epoch.

Intercurrent ovarian failure during the reproductive epoch is generally of two grades: (1) estrogenic and (2) anovulatory. Estrogenic therapy has the same indications and limitations here as when the failure originates during adolescence.

Anovulatory ovarian failure is characterized universally by sterility and not infrequently by prolonged or excessive uterine bleeding. When the patient is an adolescent or a young woman with maternal aspirations, conservative therapy designed to control excessive bleeding and secure a return of normal ovarian function should be employed. Infrequent uterine bleeding requires no therapy unless there is associated undesired sterility. Indeed, there has been too much treatment of the menstrual cycle and too little treatment of the patient.

of threatening abortions. They have been employed also in eclamptic and toxemic states. Estrogenic therapy has been employed in nausea and vomiting of pregnancy¹⁶ and for the hastening of labor.¹⁷ The rationale for their use in these conditions is based on the presumed existence of an estrogenic deficiency. This treatment has met with little success.

In eclampsia and abortion patients, estrogenic therapy has been combined with the concomitant administration of progesterone. Sodium pregnanediol glucuronide, an inactive metabolic of progesterone, administered in daily doses of 100 mg., is said to enhance the activity of estradiol benzoate and progesterone in the treatment of eclampsia.¹⁸ It is doubtful that estrogens are of benefit in antiabortion therapy. Continued and intensive research seems necessary before well-defined indications for estrogenic therapy during the pregnant state can be established.

Many obstetricians choose to stop lactation, or decrease milk formation in the case of painful engorgement of the breast, by means of estrogenic therapy. Recently, diethylstilbestrol has replaced the limited use of natural estrogens in this procedure. Its action is fast, and its toxic manifestations, however slight they may be under other circumstances, are said to be absent in the puerperal woman.^{13, 17, 19} The optimum daily dosage seems to be 5 mg. As a rule, only a few days of therapy are required for the lactating tissues to become inactive. It would appear, however, that endocrine therapy has no particular advantage in this regard over the use of ice packs and other time-honored measures.

Other Uses of Estrogens: Estrogenic therapy has been applied empirically in a number of conditions, not necessarily gynecologic in nature: atrophic rhinitis, acne and laryngeal papillomas and gonorrheal vaginitis in children. Estrogens have been administered topically in atrophic rhinitis, acne, and gonorrheal vaginitis in children on the basis of their epithelial trophic properties. Satisfactory results have been obtained in some cases of atrophic rhinitis. The results in acne have been indifferent. Estrogenic therapy of gonorrheal vaginitis in children has been outmoded by the use of the various "sulfa" drugs. Laryngeal papillomas, not uncommon in children, tend to disappear at puberty. This is ascribed to the normal increase in estrogen production at this time.²⁰ On this basis, estrone in oil was applied by spray to the larynx. Approximately 1,000 I.U. were administered in weekly treatments. Therapy covered a number of months. It was followed by a regression of some of the papillomas; inhibition of new growths was marked. Thus, it proved to be a successful adjunct to surgery in clearing the larynx of papillomas. Surgery might be unnecessary if the condition were diagnosed at its onset and estrogenic therapy applied.

Relation of Endocrine Therapy to Carcinogenesis: Reports upon the relationship of hormones to the genesis of carcinomas and other atypical growths in experimental animals have reached voluminous proportions in the last few years. Recent papers have reviewed this problem.²¹ The theoretical chemistry of the origin of malignant growths in the organism has been discussed.²²

There should be no longer any doubt regarding carcinogenic properties of hormones, especially of estrogens in the laboratory animal. Atypical growths may arise at one or in numerous sites as the result of stimulation; the genesis of these growths may be, but is not necessarily, related to a hereditary factor which favors neoplasia.²³ The formation of tumors by estrogens apparently may be prevented to a large extent if progesterone be administered concurrently with estrogens.²⁴

when administered by mouth. Small amounts given daily over a period of a few months should give satisfactory results. Hypodermic medication should be avoided; its psychological effects are bad. Estriol glucuronide, in daily doses of from 120 to 960 day oral units, has been found efficacious. Occasional patients may require larger doses. Diethylstilbestrol has had its widest use, and perhaps its most uncritical, in this group of patients. In general, the dosages employed have been too large, and treatments have been too prolonged. There are numerous instances reported of postmenopausal uterine bleeding being induced from daily doses of 1 mg. and larger. The writer agrees with those^{12, 13} who have recommended the use of diethylstilbestrol in daily doses of much less than 1 mg. in the treatment of climacteric symptomatology.

Therapeutic schedules should be designed to be palliative only in nature. Full substitutional doses frequently result in irregularities of uterine bleeding in the premenopausal patient, and delay the natural processes of sexual aging. It is our feeling that a large percentage of patients who complain of undesired symptoms at this time of life can be "cured" with reassurance and knowledge of the fact that a thorough physical examination revealed no dreaded pathology.

Vaginitis and kraurosis vulvae are relatively infrequent complications of sexual aging. Senile vaginitis often yields to estrogenic therapy. The use of vaginal suppositories containing estrogens or of orally active estrogens in relatively small doses may be followed by the desired results without the production of any rejuvenating systemic effects. In the case of kraurosis vulvae estrogenic therapy, regardless of the manner of administration, generally has been discouraging. Surgery (vulvectomy) is the most appropriate therapeutic measure. The local application of estrogenic ointments may prove effective in treating recurrent symptoms following vulvectomy.

Opposed or Antagonistic Estrogenic Therapy: On the physiologic basis of their function-reducing effects, estrogens have been applied in certain instances of hyperfunction of the pituitary and adrenal cortical hyperactivity associated with virilism. Until the advent of diethylstilbestrol no worth-while clinical results had been obtained. Recently, favorable results have been reported following therapy with diethylstilbestrol in the cases of pituitary basophilism¹⁴ and of virilism of probable adrenal cortical etiology.¹⁵ Adequacy of dosage and duration of therapy are governed by clinical and physiologic responses of the patient.

Contraphysiologic Therapy: The employment of estrogens to inhibit or prevent the estrogenic and corpus luteum functions of the ovaries (contraphysiologic therapy) has had wide application in such conditions as so-called "menstrual headaches," dysmenorrhea, and periodic breast pain. Good results have been reported by some investigators. Large doses of hormonal estrogens, usually 50,000 I.U., or larger, given intramuscularly at two- or three-day intervals during the first half of the menstrual cycle are said to be required to suppress ovarian function sufficiently for symptomatic relief. Such a schedule often leads to disturbances in the cyclicity of bleeding. Although these undesired alterations of menstruation are temporary, the treatment seems impracticable and, for the most part, without rationale.

Therapy During Pregnancy and the Puerperium: The indications for estrogenic therapy during the course of pregnancy in general are not clear-cut. Estrogens have been used in the treatment of pregnant women having histories of repeated abortions and also in the treatment

the Council on Pharmacy and Chemistry of the American Medical Association maintained as late as the early spring of 1941³³ that clinicians had not offered sufficient data to warrant the inclusion of progesterone in *New and Non-official Remedies*.

Recent investigations³⁴ indicate a possible difference between the activity of progestin and of progesterone. Such a difference, if it exists, may account, in part, for the varying opinions upon the fundamental pharmacodynamics of the corpus luteum hormone.

Unassailable evidence from various sources points out that, in some instances at least, the presence of the corpus luteum is not necessary for maintenance of normal gestation. Removal of corpora lutea from patients with early pregnancies before the time their first menstrual periods were missed, demonstrated this fact. Early establishment of the functional adequacy of the chorionplacental system may account for the continuation of pregnancy in these instances.

The supposed relaxing effect of progestin upon the uterine musculature has led to its use in the treatment of threatening abortions and in the treatment of those patients who have histories of repeated abortions. For the same reason progestin has been used in treating functional dysmenorrhea. In spite of their apparent thoroughness, however, clinical studies have not related, etiologically, corpus luteum failure or deficiency with many repeated abortions or with dysmenorrhea.

Therapy of Abortion: Numerous reports have cited the efficacy of progestin in preventing abortion. Progestin often has received credit for success when the effects of adjuvant measures, such as thyroid substance, bed rest, limitation of sexual and other activities, etc., have not been evaluated. We have not been impressed particularly with progesterone therapy in these conditions.³⁵ Our percentage of successfully treated patients has not been as high as those of some other investigators³⁶ although the dosages were comparable or larger. When pregnant women show definite evidence of deficiency in the progestational principle, i.e., decreased pregnanediol values of the urine, even the most intensive progesterone therapy fails to prevent abortion.

Therapy of Dysmenorrhea: The results of the use of progestin in dysmenorrhea when compared to those of a host of other pharmaceutical agents are equivocal. Instead of quieting the uterus (the basis for the therapy), it has been shown that progesterone may increase uterine contractility.³⁷ Moreover, it is believed generally that most patients having functional dysmenorrhea have ample corpus luteum function; this is founded upon the facts that bleeding occurs from progestational endometriums and that essentially normal quantities of pregnanediol (an excretory product of progestin metabolism) are excreted in the urine.³⁸

Use for "Afterpains": The use of progesterone therapy for afterpains is based on its presumed uterine quieting effects. It has been described as being of benefit in this condition although other and much cheaper methods have proved quite effective in years past.

In view of the foregoing statements, the question raised by Corner in 1935³⁹ shortly after progesterone had been synthesized and studied pharmacologically in experimental animals may be cited: "Here then is a definite hormone, about to be handed to the medical profession . . . what is to be done with it?" Excepting one group of gynecic disturbances, this question well might be put to us today.

Use in Prolonged or Excessive Uterine Bleeding of Functional Nature: At the present time many believe that the use of progesterone is indi-

In spite of the reported lack of evidence of malignant changes in the reproductive system of women during or following protracted estrogenic therapy,²⁵ the possibility of this occurrence should be considered, particularly when estrogenic therapy is employed in women of climacteric age. Because of clinical statistical data and the known facts regarding cancer and heredity in experimental animals, one has been cautioned not to treat with estrogens a patient who has a familial history of malignancy.

Several recent findings are of pertinence to this discussion. Atypical growths of the cervical epithelium of four oophorectomized women have been reported²⁶ following the concurrent administration of estradiol benzoate and testosterone propionate, and of estradiol benzoate, progesterone, and anterior pituitary growth hormone. The dosage was moderate and was given over periods of six to eight weeks only. The use of growth hormone was thought to have accelerated these changes. Another report²⁷ describes the cases of three women of climacteric age in whom squamous cell carcinomas were thought to have been produced by intensive estrogenic therapy. One of these patients had a familial history of a carcinoma. Instances in which the diagnosis of carcinoma was coincidental to prolonged estrogenic therapy²⁸ serve to emphasize the rationale of caution in estrogenic therapy and point out the grave need for further clarification of our concepts of carcinogenesis.

2. *Androgens*.—We associate androgens, usually, with the sexual and somatic maturation of the male, and with the subsequent maintenance of these systems in a state of functional adequacy during adult life.

A rather widespread employment of androgenic therapy, i.e., *testosterone propionate*, in the female has been based presumably upon the fact that women excrete androgens in the urine in essentially the same amounts as do men. Up to the present time, however, no clinical studies have been reported which definitely associate any functional syndrome of the female with insufficient androgenic function. Unless such a condition be demonstrated in woman, androgenic therapy of the female must be regarded as empiric and contraphysiologic in nature.

The major pharmacologic effect of androgenic therapy of woman is an "ovarian-negating" or ovarian-depressing one. Most therapeutic endeavors of an endocrine nature in gynecology have an opposite aim, that of stimulating hypofunctioning ovaries. The grave virilizational phenomena, which not infrequently are associated with androgenic therapy of women, may render it an unnecessary and unjustified form of pharmacologic mayhem.

3. *Progestational Principles*.—Experimental studies of the physiology of the corpus luteum began nearly half a century ago.²⁹ Clinical employment of corpus luteum extracts dates to some thirty years ago.³⁰ In 1934, an active principle of the corpus luteum, *progesterin*, was isolated and identified.³¹ During the same year, a compound having the chemical identity of progesterin, and accepted as having the same pharmacologic action, was synthesized from stigmasterol and from pregnane-diol.³² This substance was called *progesterone*.

A time-honored concept of the physiology of the corpus luteum attributes to it the role of protecting and nurturing the product of conception. Its active principle, progesterin, has been described as exerting a quieting relaxing action upon the myometrium. Ardent proponents and opponents of this concept base their statements upon clinical as well as experimental studies. The evidence gathered from the studies of each of the opposing groups has been so well founded, in fact, that

radical mastectomy, for example, no constant beneficial results were obtained.⁴¹

II. Endocrine Extracts of Protein or Protein-Like Nature

The substances of this nature to be discussed are the various gonadotropins and desiccated thyroid gland. The sources of these are the anterior pituitary, certain body fluids and the thyroid. Discussion of the vasopressor and oxytocic principles of the posterior pituitary will be omitted.

1. *Gonadotropins*.—These may be divided into three groups, depending upon their sources: (1) *pituitary*, extracted from the pituitary gland itself; (2) *chorionic*, extracted from pregnancy urine; (3) *equine*, extracted from the serum of pregnant mares. The ultimate source of the latter two substances is thought to be the chorioplacental system.

As yet, there are no extracts of the anterior pituitary which are sufficiently free of toxic or reaction-producing materials for satisfactory clinical use and which combine potency and practicability for prolonged therapy. This would seem theoretically to be the gonadotropin of choice.

Extracts containing chorionic gonadotropin have been employed for a number of years. A great deal of their use in gynecology has been uncritical. Despite earlier beliefs to the contrary, this gonadotropin is incapable of stimulating the follicular apparatus of ovaries of either woman or monkey. Rather, it depresses follicular and granulosa cell development, thereby depressing estrogen metabolism. In rodents, the ovarian stimulation is ascribable to changes in pituitary function and not to a direct ovarian stimulation. These gonadotropic extracts possess no hemostatic action in functional uterine hemorrhage. Apparently successful results obtained during the early days of chorionic gonadotropin development were due, probably, to a nonspecific reaction to foreign proteins.

Following the commercial advent of equine gonadotropin there developed a widespread enthusiasm regarding the therapeutic potentialities of this gonadotropin.

Despite conclusive data from studies on the rat, Engle's very true statement⁴² is pertinent: "There is no way to study human physiology other than to study human beings. Experimental animals serve only to prepare the way for human experimentation." When human experimentation is impracticable, the results usually may be mirrored in other primates. More heed should be taken of the results of critical hormonal studies made on the monkey.

Equine gonadotropin has the ability to stimulate follicular activity in the human being and in the monkey, but ovulation and corpus luteum formation are not induced in the monkey, nor has it been established that ovulation occurs upon therapy of women whose ovaries are not experiencing these phenomena spontaneously.

Gonadotropins have, in general, only one application in gynecology: treatment of the hypofunctioning ovary. If therapeutic success is to be had with gonadotropins, the following criteria must be satisfied: a state of pituitary deficiency must exist as a basis for the ovarian failure; the ovaries should not have lost their normal reactivity to gonadotropic stimuli; a system of gonadotropic therapy must be available which is adequate to evoke responses in the ovary, resulting in ovulation with the discharge of a fertilizable ovum and the production of a progestational state of the endometrium.

cated in the conservative therapy of functional uterine hemorrhage due to adolescent or intercurrent ovarian failure. In these conditions there is associated usually an absence of corpus luteum activity due to anovulatory failure. There are some clinical data to the effect that the cyclic administration of estrogen and progesterone under these circumstances may result in complete salvage. Progesterone, however, should not be regarded as an effective hemostatic agent in functional uterine hemorrhage: when given during an episode of bleeding, it increases the hemorrhage and when given during the nonbleeding phase, it may provoke bleeding. Upon occasions the statement has been made that no absolute proof had been presented that progesterone constituted an essential part of such a schedule. Recently, however, it was reported that in the treatment of patients who were bleeding from estrogenic endometriums, the use of estrogens alone was of little value in effecting complete salvage.

A few years past, another compound having progestational activity, was synthesized from estradiol: anhydro-hydroxy-progesterone.⁴⁰ It is active when administered by mouth. Patients usually can be treated intramuscularly with progestin or progesterone at less expense than with adequate amounts of anhydro-hydroxy-progesterone. In our hands it has been as efficacious as progesterone in the treatment of threatened abortion and those pregnant women having histories of repeated abortions.³⁵ The ratio between the effective dosages of orally administered anhydro-hydroxy-progesterone and progesterone given intramuscularly is probably 10 to 1.

Although many reports credit progesterone used in 1 and 2 mg. doses daily or several times weekly with therapeutic successes, it is the consensus that the daily administration of 5 mg. is usually nearer the required dosage in gynecology and that 5 to 10 mg. given daily or several times weekly seem to be nearer the therapeutic requirement when threatening abortion is being treated.

4. *Adrenal Steroids*.—Corticosterone and its related steroids may permit worthwhile applications in gynecology and obstetrics by virtue of their ability to regulate the metabolism of electrolytes and water. The acetate of *desoxycorticosterone*, the most widely used of these cortical steroids, will be discussed. It is not a complete cortical principle, however, since it lacks the carbohydrate metabolic factor.

Uses in Vomiting of Pregnancy: Desoxycorticosterone acetate may be of value in treating those patients who have become markedly dehydrated and depleted of sodium and chloride due to pernicious vomiting of pregnancy. It has been suggested the dosage be small, 1 or 2 mg. daily, and that overtreatment be avoided. Extracts of adrenal cortex have been used also in vomiting of pregnancy. The glucose mobilizing effects of these may be of value.

Use in Preparation for Adrenal Surgery: Desoxycorticosterone acetate is of value in the preoperative preparation and postoperative care of patients requiring adrenal surgery. The hazards of adrenal surgery have been reduced by a regime like the following: The patient is given desoxycorticosterone acetate intramuscularly, 5 mg. daily, beginning four days prior to the day of operation and ending several days postoperatively. Increases in dosage on the day of operation and the duration of postoperative treatment depend upon the responses and requirements of patients.

The efficacy of desoxycorticosterone acetate in protecting against surgical shock has not been established: when administered prior to

tropic therapy (to be described later) should follow at this stage. (2) Equine gonadotropin may be given in series of treatments to produce the same sexual and somatic maturation, the patient subsequently being transferred to a cyclic 1-2 gonadotropic schedule.

Use of Cyclic 1-2 Gonadotropic Therapy in Anovulatory Failure: The cyclic 1-2 gonadotropic schedule attempts to duplicate the hormonology of the menstrual cycle and takes into account a likely synergism of the follicle-stimulating and luteinizing gonadotropin fractions. It embraces the sequential and cyclic use of equine gonadotropin for its follicle-stimulating properties (follicle-stimulating hormone) and chorionic gonadotropin for its luteinizing ability (luteinizing hormone). The therapeutic schedule is as follows: Beginning on the fifth day of the cycle equine gonadotropin is given intramuscularly in daily doses of 400 I.U. for ten days; beginning on the sixteenth day of the cycle, chorionic gonadotropin is given intramuscularly in daily doses of 500 I.U. for ten days. We, and others, have found this form of therapy to be effective in inducing ovulation in some patients with anovulatory ovarian failure.

Anovulatory failure during the reproductive years is characterized by regular or irregular bleeding from estrogenic endometriums. This type of ovarian failure is associated with sterility since its existence is ascribable to the nonoccurrence of ovulation. It is not associated necessarily with any degree of estrogenic deficiency. Therapeutic endeavors under these circumstances are usually for one of two reasons: (1) to control excessive or prolonged uterine hemorrhage and to initiate fertile ovarian cycles, or (2) to circumvent undesired sterility alone.

Gonadotropic therapy is of no real value in correcting infrequent or excessive uterine bleeding. Therefore, when confronted with these symptoms of anovulatory ovarian failure, regulation of flowing may be secured by employment of the cyclic estrogen-progesterone schedule previously detailed in the discussion on estrogens. When cyclic bleeding has been established and occurs from a progestational endometrium, the patient may be given a trial of cyclic 1-2 gonadotropic therapy during a succeeding cycle.

Patients, whose therapy is designed to combat their endocrine sterility and whose bleeding is cyclic, are given a preliminary series of cyclic estrogen-progesterone therapy to assay their endometrial reactivity (biopsy at onset of bleeding) before cyclic 1-2 gonadotropic therapy is started. If the response to a series of cyclic 1-2 gonadotropin therapy be negative, a second trial is made, with a doubling of dosage. This second series, however, should follow a rest cycle. Lack of response after the second trial of therapy probably indicates the existence of refractive ovaries.

In the case of those patients who respond to cyclic 1-2 gonadotropic therapy (i.e., bleed from progestational endometriums as judged from biopsy) no further immediate treatment should be given. Instead, the possibility of spontaneous adjustments of ovario-pituitary and ovario-endometrial reciprocities should be investigated. The status of the endometrium at the onsets of episodes of bleeding should be the criterion for judging normal recovery of these relationships. Several cycles should be allotted for such alterations.

Spontaneous adjustments of these reciprocities indicate no need for further therapy. However, if menstrual bleeding (bleeding from a progestational endometrium) does not occur spontaneously after the initial response to cyclic 1-2 gonadotropin therapy, further treatment is required. Since, at the present time, it is impracticable to substitute

In general, gonadotropic therapy has these limitations and undesirable qualities: (1) A patient may be allergic to these protein or proteinlike substances. This possibility necessitates skin testing each prospective patient prior to therapy. (2) Continued treatment with these substances results in antibody formation with eventual refractivity to the hormone. Rest periods are required, therefore, between courses of therapy. (3) Sensitivity to these extracts sometimes develops after the completion of a course of treatment. This may cause a final cessation of this form of therapy. A near fatality under these circumstances following intravenous administration has been reported.⁴³ (4) Administration must be by injection. (5) The hormone is destroyed rapidly or excreted promptly after administration, making a functional level which characterizes that of normal physiology extremely impracticable to maintain. (6) Inability to regulate bleeding; in the case of patients with irregular bleeding, cyclicity must be maintained by the use of ovarian steroids. Irregular bleeding often is produced by gonadotropic therapy in women having regular cycles.

Although therapy with gonadotropins has these rather serious encumbrances, there are two general types of patients which may be treated successfully with this form of therapy: the patient with adolescent hypoovarianism and the sterile patient with anovulatory cyclic (or acyclic) bleeding.⁴⁴

Use of Equine Gonadotropin in Adolescent Estrogenic Failure: Equine gonadotropin is recommended for an initial trial of therapy since it has been shown to be the most potent gonadotropin available with regard to stimulation of the granulosa apparatus, i.e., the elaboration of estrogens. A suggested therapeutic schedule in the case of a patient with adolescent estrogenic failure is the following: If the skin test has proved negative, the patient is given 200 to 400 I.U. of equine gonadotropin daily, intramuscularly, for a period of four to six weeks. One series of treatments should not continue longer than this length of time and a respite of four to six weeks from therapy should follow. Should no response occur during the first series of treatment, a second series may be given with the daily dosage increased to 1,000 I.U. Positive responses are characterized by evidences of increased elaboration of estrogens by the ovaries: enlargement of breasts, uterus, vaginal canal, ovaries, changes in vaginal smears, proliferation of the endometrium and withdrawal bleeding. If no responses are observed during this second trial, it is justifiable to conclude that the ovaries are refractive to gonadotropic stimuli. The remaining alternative then is treatment of those patients who do not respond to gonadotropic therapy with full substitutional doses of estrogens.

It has been noted that marked ovarian enlargement may occur during therapy with equine gonadotropin. When this occurs, treatments should be stopped, but these may be resumed at a lower dose level after a rest period, the duration of which should be determined by ovarian regression. This fact requires repeated bimanual examinations during the course of therapy.

When a patient with adolescent estrogenic failure responds to gonadotropic stimulation, sufficient time should elapse before further treatment in order to determine whether or not there will be a spontaneous and complete recovery of ovarian function. If this recovery fails to occur, one of two methods of treatment may be employed. (1) Estrogens in substitutional doses may be used to bring about adolescent maturation or a state of functional adequacy. Cyclic 1-2 gonado-

so-called goiter areas. It is well known that the adequate use of thyroid in these areas reduces the abortion rate.

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at the pituitary level over extended periods, cyclic 1-2 gonadotropic therapy should be reserved for periodic trials for pregnancy. Those patients who had been concerned only with sterility should need no treatment between these trials, while those, who had had an irregularity of bleeding as well as sterility, may require continued supervision with regard to the regulation of uterine bleeding with cyclic estrogen-progesterone therapy.

When pregnancies are secured as the result of cyclic 1-2 gonadotropic therapy, there is a likelihood of the occurrence of early abortions. It is advisable, therefore, to begin active antiabortal therapy with appropriate adjuvant measures when pregnancy is diagnosed.

Therapy of Relative Corpus Luteum Failure: Relative corpus luteum deficiency may be reflected in shorter menstrual periods than normal, bleeding from poorly differentiated pregestational endometria and sterility sequential to this inadequate preovulatory preparation of the endometrium for the fertilized ovum. If this relative deficiency in corpus luteum function be due to insufficient gonadotropic stimulation, the employment of chorionic (luteinizing) gonadotropin may induce satisfactory responses. These responses may be reflected in the lengthening of the pregestational (luteal) phase of the cycle, an increase in progestin metabolism and in more complete preovulatory preparations of the endometrium. The suggested dosage of chorionic gonadotropin in this endeavor is 500 I.U. administered daily for ten days beginning on the fifteenth day of the cycle.

It is my opinion that, at present, the endometrial biopsy method cannot be dispensed with in evaluation of results of the therapeutic schedules, described in this section. Studies of the urinary pregnandiol excretion in conjunction with these therapies provide confirmatory evidence only if the results obtained agree with the concurrent endometrial findings.

2. *Thyroid Substance.*—The little understood but effective role of thyroid substance in gynecologic and obstetric therapy has stood well the trials of time. Its effects upon the reproductive apparatus of woman, however direct or indirect the action may be, are profound and varied. Minor grades of hypometabolism may result in significant impairment of ovarian function.

Use in Amenorrhea: Thyroid substance has been used empirically in the treatment of patients having intercurrent ovarian failure associated with the absence of uterine bleeding. Not only does bleeding occasionally follow this form of therapy but also patients may become pregnant during therapy. These patients most likely had thyroid deficiencies and under these circumstances, their thyroid therapy was rational.

Use in Functional Uterine Hemorrhage: Because of its presumed hemostatic properties, thyroid substance has been used in functional uterine bleeding of prolonged or profuse nature. In severe cases its action may be too slow for immediate results. It may be of value when used concurrently with cyclic estrogen-progesterone therapy in regulating acyclic and excessive bleeding when this is due to hypothyroidism.

Use in Endocrine Sterility: It is considered generally to be wise therapy to give sterile women, in whom no absolute cause for sterility has been found, a full therapeutic trial of thyroid substance, even though their basal metabolic rates may not be low.⁴⁵ Hypothyroidism is a common cause of sterility. It may act by precipitating anovulatory failure or it may impair the development of ova without significant endocrine manifestations.

Use in Abortion: Thyroid deficiency as an etiologic factor in abortion is demonstrable by the high percentage of abortions occurring in the

tions, as heretofore, are excellent. The book may be classified as intermediate between a textbook and a compend.

R. T. FRANK.

Obstetrics

This monograph, **Principles of Extraperitoneal Cesarean Section**³ by Dr. James V. Ricci and Dr. James P. Marr, has been written to advance the extraperitoneal principle of cesarean section, particularly, the Physick-Selheim procedure.

The authors feel that this type of operation gives the maximum of safety to the mismanaged parturient and should supplant the Porro section, craniotomy, and Dührssen's incisions and those types of instrumental vaginal delivery which are accompanied by trauma and its end results. They pay special tribute to those German obstetricians who brought to fruition the suprasymphysial technique in surgical obstetrics.

The original suggestion of such a mode of approach was originally suggested by Physick. In the intervening years many methods of attack on the obstructed and potentially or actual infected parturient had been proposed. Selheim's efforts are high in the development of the truly extraperitoneal approach to the uterus. The senior author of this monograph has made an important contribution in his proposed technique.

The historical and earlier types of operation have been discussed. For a clear understanding of the anatomic relationships involved in this particular operation, there are two chapters which are devoted to the relationships of the isthmus and the lower segment and the transversalis fascia, and its anatomic details. Methods of delivery in the extraperitoneal cesarean section, as well as wounds infected and methods of drainage, are described.

There is a review of the various techniques of extraperitoneal approaches concluding with the very recently suggested techniques of both Waters and Ricci, the senior author. The operations proposed by the latter two are thoroughly illustrated. These illustrations together with the diagrammatic representations of the pelvic, fascial, and peritoneal relationships found in the section on anatomy, should enable anyone familiar with pelvic surgery to follow successfully the technical steps proposed.

The essential factors in the execution of the Physick-Selheim extraperitoneal cesarean section are again given with marked detail in a complete description of a typical operation. The performance of the operation in patients who have had previous pelvic or cesarean operations is discussed with regard to the difficulties which might be produced by adhesions. The closing chapter deals with complications which may be met during the operation or postoperatively. The appendix presents some statistics and a large bibliography.

The spreading recognition of the value of this type of approach for delivery, particularly, in a potentially or actually infected obstructed labor, should make this book of inestimable value to all practicing obstetricians.

PHILIP F. WILLIAMS.

This timely contribution, **Urological Diseases of Pregnancy**⁴ by Dr. Crabtree, brings together his own experience, the many publications on the urology of pregnancy, and the practical interpretation of both. Dr. Crabtree refers quite fittingly

³**Principles of Extraperitoneal Cesarean Section.** By James V. Ricci, M.D., Associate Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc., and James Pratt Marr, M.D., Associate Attending Surgeon, Women's Hospital in the State of New York, etc. 47 illustrations, 224 pages. Blakiston Company, Philadelphia, 1942.

⁴**Urological Diseases of Pregnancy.** By E. Granville Crabtree, M.D., Urologist to the Boston Lying-In Hospital. With a chapter by George C. Prather, M.D., Assistant Urologist to the Boston Lying-In Hospital. 158 illustrations, 472 pages. Little, Brown and Company, Boston, 1942.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

Dr. Schauffler's monograph on *Pediatric Gynecology*¹ represents the experience of seventeen years in this type of work. Since the major textbooks on gynecology and pediatrics have presented only brief notice of gynecologic lesions of the adolescent, a book of this nature is welcome. Dr. Schauffler stresses the psychologic factors in the management of very young children when methods of investigation or treatment of the genital organs are necessary.

Regionally, he takes up the external genitals, the cervix, and other areas. Since both estrogens and sulfanilamides have been accredited in recent years with high praise in the treatment of vaginitis in childhood one looks for Schauffler's comparisons of these two lines of treatment. He states that there is an optimistic future for the use of sulfathiazole. The observations thus far reported are small and, he adds, the advances with the use of estrogenic substances should not be discredited. He feels that there is no contraindication for the combining or alternating their use. He feels that nonspecific infections appear to react more readily to estrogenic substances.

In discussing the disorders of adolescence, Schauffler refers to the various hormones which have been recommended, but suggests that one should be coldly analytical of the value of endocrines in the treatment of dysmenorrhea. The surgical conditions of the pelvis and lower abdomen in young children are well handled. The section on general surgical conditions has been written in collaboration with Dr. Brunkow. There are special chapters devoted to urologic and proctologic diseases which assemble many scattered observations and methods found in the literature.

Of very practical value to those who handle pediatric gynecology, even occasionally, is a chapter on the social service aspects of this condition; the same may be said for the chapter on medicolegal aspects. These two chapters take up and suggest solutions for the side problems which at times are found extremely difficult to handle.

There is an appendix on the standards of commercial hormone preparations and another on state agencies administering child welfare. This book should fulfill a long felt need both from a broad viewpoint of the subject matter as well as the many practical points suggested in diagnosis and technique of treatment.

PHILIP F. WILLIAMS.

*Diseases of Women*² by Ten Teachers, under the direction of Clifford White, has reached its seventh edition in twenty-three years. Apparently this is a very popular elementary textbook in England. In general, it resembles the previous editions. The use of sulfanilamide in inflammatory conditions has been added; the classification of ovarian tumors has been simplified but still proves unsatisfactory. The illustra-

¹*Pediatric Gynecology*. By Goodrich C. Schauffler, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School. 65 illustrations, 384 pages. The Year Book Publishers, Inc., Chicago, 1942.

²*Diseases of Women*. By Ten Teachers. Under the Direction of Clifford White, M.D., B.S. (Lond.), F.R.C.P. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. Edited by Sir Comyns Berkeley, Clifford White, and Frank Cook. Seventh Edition. 435 pages. The Williams & Wilkins Company, Baltimore, 1942.

The Prospective Mother⁶ by Dr. J. Morris Slemmons, appears in a fourth edition. The first edition appeared in 1912, and it is interesting that in this year, 1912, the pamphlet on *Prenatal Care* for the Children's Bureau was also issued. Dr. Slemmons' book has been one of the standard texts for women during pregnancy for thirty years, and its revisions have kept it up to date. There are very few questions asked by a pregnant woman for which the answers could not be found in this book. The text contains helpful advice and counsel. The technical material is clear and concisely given, and in sufficiently simple terms that the average woman should easily understand it. Dr. Slemmons has included a short discussion of many of the recent advances in obstetrics, stripped of unnecessary verbiage, so that the patient may know the newer methods. An excellent chapter on the care of the newborn, contributed by Dr. Phillip E. Rothman, has been added. This section contains many useful hints for the recent mother in caring for her child.

This is an outstanding book for the education of the laity in maternity hygiene and should retain its popularity in this fourth edition.

PHILIP F. WILLIAMS.

Endocrinology

Glandular Physiology and Therapy⁷ is a symposium prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. There are thirty-one chapters which appeared in the *Journal of the American Medical Association*. Previous editions were published in 1927 and 1935. Only a small number of contributors to the previous editions contributed to this volume. The articles cover every phase of endocrinology, including the Internal Secretions of the Gastrointestinal Tract (Ivy) and the Present Status of Commercial Endocrine Preparations (Freed).

The volume is extremely hard to analyze. It does not, for example, pretend to cover the ground such as one finds in *Physiological Reviews*, nor does it attempt to give a didactic summary of our present knowledge. Several of the authors have used this medium to broadcast their own studies and views, even if such are not generally acceptable. The ground covered is enormous. In some of the contributions, minutiae are detailed, in others, merely a general outline is given. I greatly doubt whether the non-specialist can gain by wading through its pages. On the other hand, the investigator and the endocrinologist will be hampered by the fact that there is no index of authors. It certainly cannot be used as a textbook because of its disjointedness. Therapy, on the whole, has not been sufficiently featured.

In spite of the many disadvantages pointed out, the symposium must be considered as a valuable contribution because leaders in the various branches of this now enormous field, have placed their views on record and have given the references, mainly of their own work, upon which they have formed their concepts. The symposium likewise makes evident how rapid advances in this field are and how rapidly our preconceived notions constantly require revision.

R. T. FRANK.

The second edition of Werner's **Endocrinology**⁸ is a well-written and well-planned textbook which fully covers the subject. It is profusely illustrated, contains eighty-

⁶**The Prospective Mother.** By J. Morris Slemmons, M.D., Consultant, in *Obstetrics and Gynecology*, The Hospital of the Good Samaritan, Los Angeles, California. With a Chapter on Care of the Newborn. By Phillip E. Rothman, M.D., Professor of Clinical Pediatrics, University of Southern California. Fourth Edition. 264 pages and 16 illustrations. D. Appleton-Century Company, New York and London, 1942.

⁷**Glandular Physiology and Therapy.** A Symposium, prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. American Medical Association, Chicago, 1942.

⁸**Endocrinology.** Clinical application and treatment. By August A. Werner, M.D., assistant professor of internal medicine, St. Louis University School of Medicine, etc. Second edition, thoroughly revised. Illustrated with 327 engravings and a colored plate. 924 pages. Lea & Febiger. Philadelphia, 1942.

to the dual origin of this subject, and discusses from the standpoint of obstetrics the changes taking place during pregnancy which have an influence on the urologic system. The reversal of this then brings out the anatomy and physiology of the urinary tract in relation to pregnancy.

In the consideration of the interdependence of the condition, pregnancy and of the urologic system in relation their anatomy and physiology, one finds a well-developed explanation for the factors, endocrine and others, which lead to functional changes and infections of the urinary tract in pregnancy. The remainder of Part I gives a comprehensive discussion of such infections and their treatment. Thirteen pages are devoted to a consideration of the use of the sulfonamide drugs in the infection of the urinary tract during pregnancy. The literature has been extensively covered and the text on this subject leaves practically no angle of the use of these drugs untouched.

The surgical treatment of the urinary tract infections is described in detail. The research worker in this field will find much of interest in the two chapters on "pregnancy in animals in relation to the urinary tract" and "pyelonephritis in animals."

Part II of the book discusses toxemia of pregnancy, which is a signed chapter by Dr. George C. Prather. In this chapter the relationship of the various urologic lesions to the symptom complex, toxemia of pregnancy, is thoroughly discussed. Prather feels that pyelography has not yet assumed its proper place in the differential diagnosis of the toxemias. He develops his discussion on the classification proposed by the American Committee on Maternal Welfare, which he states has been accepted by the Washington Conference on Toxemias. Among the other topics in Part II are found a consideration of tuberculosis, the tumors and congenital conditions of the kidneys as well as injuries, technique of laboratory tests and use and their evaluation. There is a very clear statement as to renal contraindications to pregnancy.

The book is beautifully illustrated. There are many retouched roentgenograms, urograms, and photomicrographs. The bibliography appended to each chapter has been combined at the end of the book and covers the important contributions of many years. There are 73 pages of references in the bibliography. It seems surprising that this book has not appeared long since. It has remained for the author to fill this want in a book which will be constantly referred to by all urologists, obstetricians, laboratory workers, and surgeons.

PHILIP F. WILLIAMS.

Contraception and Fertility⁵ was written under the auspices of the National Committee on Maternal Health. It is a study based on empirical observations of thirteen hundred families in Logan County, West Virginia. Its object was to determine "what is the likelihood that rural women of high fertility can be encouraged to practice birth control?" The site of the study was a community which represents frontier, agriculture, and coal industry, consisting of isolated coal camp communities under the control of operators. "Conditions in these coal camps have helped to perpetuate the isolation, the ignorance, and the inflexibility of the mountaineer." In such environments, it is not surprising that there are few hospital beds and primitive conditions. The contraceptive used was of the simplest, namely vaginal jelly with an applicator. This study is not a final one nor are the results obtained to be considered final. The project appears to be invaluable and worth while.

R. T. FRANK.

⁵**Contraception and Fertility in the Southern Appalachians.** By Gilbert Wheeler Beebe, Ph.D., Former Statistician, National Committee on Maternal Health; Research Memorial Fund. 274 pages. Medical Aspects of Human Fertility by the National Committee on Maternal Health. Published for the National Committee on Maternal Health, Inc., by The Williams & Wilkins Co., Baltimore, Md., 1942.

cases Control. It is not a laboratory book but should be of interest to serologists because of the discussion of the development of such tests particularly discussion in regard to sensitivity and specificity levels.

There is an appendix dealing with serology in syphilis control so far as it concerns the health officer and the industrial physician. The discussion concerning sensitivity and specificity of various tests should interest those who are concerned with syphilis control as it is now practiced in premarital and prenatal situations. From copies of orders of the army and navy medical bureaus it appears that the Kahn test is the one now used for examination of all blood specimens to be tested for syphilis in the military departments.

PHILIP F. WILLIAMS.

Blood Grouping Technic,¹² by Fritz Schiff and William C. Boyd, is a laboratory manual for all those who are concerned with this problem of medicine. There is an interesting foreword by Karl Landsteiner. The book is entirely technical and is devoted to directions for carrying out blood grouping tests. The details are clear and concise and their application to clinical medicine are thoroughly considered. There is a short section on the theoretical foundations, after which the authors discuss the general technique of blood grouping investigations, and continue with the special applications.

Of particular interest to obstetricians might be the section on the Rh factor and its significance. The remarks on blood banks, the caution offered regarding the actual transfusion, particularly the patient's condition during the first minutes of the transfusion, and preparation of such blood substitutes as serum and plasma. Again, the obstetrician should be interested in the section discussing problems of relationship including disputed paternity, in which the technical and legal aspects are fully reviewed. In view of the widespread use of blood and its substitutes in modern medicine, this book should have a general appeal to those working in clinical laboratories.

PHILIP F. WILLIAMS.

Sex Fulfillment in Marriage,¹³ by the Groves family (Professor, Mrs. and Miss) with an introduction by Robert A. Ross and illustrated by Robert L. Dickinson, has very many commendable features. Dr. Groves is credited with having given the first college course on preparation for family life. In this well-written, unpretentious book, the normal individual and the normal conditions are featured, in contrast to so many books on the same subject in which abnormalities are brought to the fore.

Few people are prepared for marriage; hence much unnecessary and avoidable blundering. Today more and more colleges give courses, mainly at the request of their students. Factors which play a great role are ignorance, fear of lack of control before marriage, the common concept that sex is associated with evil, exaggeration of the feeling of penitence for premarital happenings are some of the content. Social maturity and sex maturity do not keep step with each other. Difficulties arise from these discordancies. The common ways that youths meet their problems are retreat, indulgence in sex play (petting), and premarital sex indulgence. Courtship, its difficulties and hazards, the anatomy and physiology of sex, and starting marriage are contained in some of the other chapters. After marriage,

¹²**Blood Grouping Technic.** By Fritz Schiff, M.D., Late Chief of Department of Bacteriology, Beth Israel Hospital, and William C. Boyd, M.D., Associate Professor of Biochemistry, Boston University School of Medicine, etc. With a Foreword by Karl Landsteiner, Rockefeller Institute for Medical Research. 248 pages. Interscience Publishers, Inc., 215 Fourth Ave., New York, 1942.

¹³**Sex Fulfillment in Marriage.** By Ernest R. Groves, Professor of Sociology, University of North Carolina, Gladys Hoagland Groves and Catherine Groves. Introduction by Robert A. Ross, M.D., Associate Professor of Obstetrics and Gynecology, Duke University, School of Medicine. Illustrated (By Robert L. Dickinson, M.D.). 319 pages. Emerson Books, Inc., New York, 1942.

six case histories and a wide footnote reference to the literature. This edition, just as the previous one, appeals to the student, physician and allied professions, covering normal and abnormal physiology of the endocrine glands, the physical types resulting from deviations, and particularly the diagnosis of endocrine symptoms. There is an excellent balance between the underlying experimental work which is clearly and impartially described, and the clinical aspects of the various diseases, diagnosis, and therapy.

R. T. FRANK.

Hamblin's small monograph on **Facts for Childless Couples**⁹ is written for the well-educated laity. It is concise, factual, well planned and well illustrated. It should save many a couple from falling into the hands of charlatans and near-charlatans, many of whom practice in this field, particularly in its specialized portion of artificial insemination.

R. T. FRANK.

Miscellaneous

Diseases of Metabolism,¹⁰ including detailed method of diagnosis and treatment, is a large (nearly one thousand pages) textbook for practitioners, edited by Garfield G. Duncan¹⁰ together with fifteen contributors, well known in their field. In order to cover the subject, endocrinology, nutrition, the vitamins, and hematology are considered. There is a short introduction by the late Dr. Banting.

"A practical consideration of the physiology of metabolism, the pathological physiology as observed in various diseases of metabolism, and the methods of detecting and of treating these disturbances is presented." Fundamentals, recent investigative work, chemical and physiologic methods are described in detail. A number of valuable charts and tables are appended. The subject matter does not permit of detailed review. There are sixteen chapters which cover every aspect of the field. Garfield Duncan discusses the basal metabolism in general, hyperinsulinism, diabetes insipidus, and diabetes mellitus, as well as the Appendix. Carbohydrate metabolism is described by Long of Yale; proteins and lipids by Abraham White; mineral metabolism by Cantarow; water balance in health and disease by Peters. The nutritional and metabolism disorders of the blood are handled by Tocantins. Spies and Butt deal with the vitamins and avitaminoses; Newburgh with undernutrition. Frank Evans describes obesity which in every instance appears to be based on overfeeding, no matter what outside causes contribute. The chapter on xanthomatoses and allied diseases was written by Mason; that on gout by Walter Bauer and Friedrich Klemperer. From this it is evident that this book should prove of great use to anyone interested in the details of metabolic disorders. Both the detailed index and a short chapter bibliography increase the value as a book of reference.

R. T. FRANK.

This volume, **Serology in Syphilis Control**¹¹ by Reuben L. Kahn, represents an amplification of six lectures delivered to physicians at the military medical schools in Washington and the University of Michigan during the courses in Venereal Dis-

⁹**Facts for Childless Couples.** By E. C. Hamblen, Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief of the Endocrine Division of the Department of Obstetrics and Gynecology and Endocrinologist, Duke Hospital, Durham, North Carolina. 103 pages. Charles C Thomas, Springfield, Illinois, 1942.

¹⁰**Diseases of Metabolism.** Detailed Methods of Diagnosis and Treatment. Edited by Garfield G. Duncan, M.D., Chief of Medical Service "B", Pennsylvania Hospital, Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pa. 155 illustrations and 7 plates in color, 985 pages. W. B. Saunders Company, Philadelphia, 1942.

¹¹**Serology in Syphilis Control.** With an appendix on the use of serology by military officers and industrial physicians. By Reuben L. Kahn, M.D., Chief of the Venereal Disease Clinical Laboratories and of Serologic Consultation Service of the Pennsylvania Hospital, etc. 206 pages. The Williams & Wilkins Company, Baltimore, 1942.

In this new work, *Clinical Anesthesia, A Manual of Clinical Anesthesiology*,¹⁶ Dr. Lundy offers a comprehensive discussion of the various anesthetic agents, their nature, their uses, and the techniques. Dr. Lundy's position in the field of anesthesiology is well recognized, and his presentation may be regarded as authoritative.

Sections are devoted to the choice of anesthetic agents in regional surgery and takes up in succession local anesthesia, spinal anesthesia and its various aspects. A large bulk of the book is devoted to a consideration of general anesthesia by volatile and gaseous agents. Short sections consider the less frequent modes of administration of anesthesia. There is much of a practical nature in the chapters on anesthesia and nonsurgical conditions, and in the chapter on resuscitation. Statistics have been presented, as well as the chemical bases of the agents and their chemistry in the body.

Of interest to the obstetrician is the chapter on inhalation anesthesia in obstetrics. There are additional references to the use of various agents and techniques in obstetrics and gynecology constantly through the text. A discussion on analgesia in normal labor brings out a comparison of the various agents in use at the present time. He states that the pregnant woman tolerates most methods of anesthesia well. He does not recommend spinal anesthesia for Cesarean section. Dr. Lundy's expression of his personal views and experience regarding anesthesia and analgesia in obstetrics together with the excellent analysis of the literature in these two particular fields should make the book a valuable addition to the library of the obstetrician and gynecologist.

PHILIP F. WILLIAMS.

*War Gases*¹⁷ deals with the detection, sampling, and identification of chemical warfare agents, as well as the decontamination of areas and materials polluted by them. This information is particularly useful to gas identification officers, war gas chemists, decontamination officers and health officers. Five of the chapters should prove of value to air raid wardens as well. The detailed chemistry, the methods of identification, and the many tests, however, appeal mainly to the specialist.

Today civilians are as much exposed to the hazards of warfare as are the Army and Navy. The protection of civilians must be carefully worked out, as they produce the material for the fighting forces. Although chemical warfare has played a subsidiary part, as yet, in this war, there is no guarantee that it may not be resorted to at any time. The main effects of war gases are the alarm produced, the effect on morale, the casualties, the interference with production, and the spoiling of supplies, inclusive of foods.

This book which gives not only such tests as the "sniff test," but also field and laboratory tests as well as detailed directions for recognizing contamination and most detailed instructions concerning how to go about decontamination of areas and food, is a most timely contribution.

R. T. FRANK.

The barbaric bombing of London with its destruction of the Royal College of Surgeons Building caused an irreparable loss in the museum material. Priceless collections of surgical instruments were completely destroyed as well as the valuable records which described them. Fortunately, Dr. C. J. S. Thompson, the Curator, had thoroughly studied this material and prepared a comprehensive survey which is now offered in a beautiful format entitled, *The History and Evolution of Surgical In-*

¹⁶*Clinical Anesthesia. A Manual of Clinical Anesthesiology.* By John S. Lundy, B.A., M.D., Head of Section on Anesthesia, Mayo Clinic. 735 pages and 266 illustrations. W. B. Saunders Company, Philadelphia and London, 1942.

¹⁷*War Gases. Their Identification and Decontamination.* By Morris B. Jacobs, Ph.D., Formerly Lt. U. S. Chemical Warfare Service Reserve. 180 pages. Interscience Publishers, New York, 1942.

common marital problems, hygiene, birth control, pregnancy and childbirth are discussed. Throughout this book, a high level of approach and worthy purpose are disclosed.

R. T. FRANK.

Married Life in an African Tribe¹⁴ by I. Schapera is a careful study by a well-trained anthropologist, familiar with the conditions and languages of the region. There is a long and very worth while introduction by Bronislaw Malinowski, which, contrary to the usual introduction, deserves careful reading.

This book has been designed for the general laity. It deals with the tribal customs of the Kgatla tribe which lives on what corresponds to a reservation, situated between the Transvaal and the Bechuanaland Protectorate. Some fourteen thousand natives occupy thirty-six hundred square miles of rolling country, residing in towns and villages, traversed by one railroad and rural roads. Forty per cent of the men yearly go out for wage labor. The main interest of this careful study is the fact that here is a native tribe which for one hundred years has been in contact with Europeans. The author has carefully studied the change from the ancient customs to the modern ones, due to this contact. Polygamy has greatly declined. Bachelors and old maids are practically unknown. Cousin marriages are preferred. Through the years, chastity among the young people has declined so that premarital sex relations are the rule and not the exception. Concubinage is well recognized. The extra-marital sex relations are only taken into serious consideration if pregnancy results. The author has lived among these people, has studied them closely, sympathetically and intimately. This is a well worth while and serious anthropologic contribution.

R. T. FRANK.

The second edition of the **Autonomic Nervous System**¹⁵ by James C. White and Reginald H. Smithwick has appeared after an interval of six years. There is an introduction by Walter B. Cannon. This subject has proved of increasing importance in various branches of medicine, particularly in neurosurgery, in disturbances of the peripheral vascular system, as well as in derangements of the pelvic organs. Much that is new has accrued in the interval between the appearance of the first and second editions. The authors have acquired a large clinical experience in various hospitals of Boston. In order not to increase the size of the volume, a number of deletions and changes have been made. An excellent anatomic and physiologic discussion of the autonomic nervous system and the tests required to determine disturbances form Part I. The second portion deals with the disturbances of the peripheral vascular system of the head, brain, meninges, and spinal cord, as well as the heart and aorta. Next, hypertension, disturbances of the lung ascribable to the autonomic, of the gastrointestinal tract and of the urogenital tract are dealt with in Part II. Part III covers resection of the cervical, thoracic, and abdominal sympathetics. Periarterial sympathectomy and denervation, injection of the paravertebral nerves as well as relief by crushing the mixed nerves of the lower extremities, are described. This book contains numerous illustrations and graphs, and a number of case histories. It is of interest to many branches of medicine.

R. T. FRANK.

¹⁴**Married Life in an African Tribe.** By I. Schapera, professor of social anthropology in the University of Capetown. With an introduction by Bronislaw Malinowski. Illustrated. 364 pages. Sheridan House, New York, 1942.

¹⁵**The Autonomic Nervous System. Anatomy, Physiology, and Surgical Application.** By James C. White, M.D., Assistant Professor and Tutor in Surgery, Harvard Medical School; Chief of Neurosurgical Service, Massachusetts General Hospital, Boston, and Reginald H. Smithwick, M.D., Instructor in Surgery, Harvard Medical School, Assistant Visiting Surgeon, Massachusetts General Hospital. Second Edition. 469 pages. The Macmillan Company, New York, 1941.

obstetric department at the University of Michigan, and final settling down in practice in California.

The author has a very understanding and sympathetic view of human nature and pictures the many contacts he has had with delightful frankness and abandon.

R. T. FRANK.

This new medical dictionary, **Taber's Cyclopedic Medical Dictionary**,²² a small compact volume of 1,500 pages, double column, contains approximately 60,000 words. The pronunciation and common usage is given, diphthongs have been eliminated and definitions stand out in concise statement. The pagination is by letter headings in order to provide for future expansion. The interesting feature of the book is the inclusion of 93 appendices which cover anatomic tables, unit measures in many systems, equivalents and derivatives, as well as an extensive appendix on dietetics, foods, and food values. The book closes with 16 pages of questions and answers outlined in five languages which have been especially arranged for diagnosis. The concise, compact presentation of this volume should make it useful for physician, medical student, and nurse.

PHILIP F. WILLIAMS.

The fifteenth revised edition of **Stedman's Practical Medical Dictionary**²³ has been prepared by Dr. Stanley T. Garber of the University of Cincinnati College of Medicine. The entire work has been reset and many additions and corrections made. The many additions to medical nomenclature through the advances in special fields make it essential that authors and editors consult an authoritative manual for clarity and definition of medical terms. Reference to both journals and textbooks still discloses much confusion. Simplicity and correct spelling, with the elimination of useless diphthongs and word endings, and the substitution of English for foreign words when possible, is afforded by this excellent and well recognized work which may without question be regarded as a standard reference book for the library of medical practitioners and authors.

GEORGE W. KOSMAK.

The second edition of the **Directory of Medical Specialists**²⁴ has just appeared. Since the publication of the first directory, some four thousand names of new diplomates have been added. During the interim, likewise, three new certifying Boards have been established, namely those on Anesthesiology, Plastic Surgery, and Neurological Surgery. On glancing through the directory, a number of prominent men who evidently have not made any effort to qualify, have been omitted. For this reason, the introduction states "For the present, the fact that a man's name does not appear on the lists of this Directory does not necessarily indicate, if he specializes, that he is not qualified to do so."

This large volume of 2,495 pages contains an alphabetical list and likewise separate lists under each Board, geographically arranged. Each name contains details of the special training, including internships, fellowships, residencies, and assistantships. In addition, the hospital and teaching positions, as well as government appointments, are included. Preceding each group is a short description of the organization, purposes, examinations, etc., of each Board.

R. T. FRANK.

²²**Taber's Cyclopedic Medical Dictionary.** By Clarence Wilbur Taber and Associates. 273 illustrations, second edition. F. A. Davis Company, Philadelphia, 1942.

²³**Stedman's Practical Medical Dictionary.** Fifteenth edition entirely reset and fully revised by Stanley Thomas Garber, M.D. Williams and Wilkins Co., Baltimore, Md., 1942, with thumb index, price, \$7.50.

²⁴**Directory of Medical Specialists,** Certified by American Boards, 1942. Published for the Advisory Board for Medical Specialties. 2495 pages. Columbia University Press, New York, 1942.

struments.¹⁸ This record will help to preserve the history of the development of surgical technique.

It consists of some 100 pages beautifully illustrated by drawings and photographs of many types of surgical instruments ranging from scalpels, amputation knives, and saws to operating tables. In each of the twelve chapters Dr. Thompson has discussed the history of a class of instruments, and their evolution through the ages into fairly modern times. He has chosen from the obstetric and gynecologic instruments the vaginal dilator and speculum, which apparently do not date beyond the early centuries of the Christian Era. It is probable that the dilators were used in the cervix as well as in the vagina for dilating the pelvic canal. The tubular type of vaginal dilator has outlived the multivalved and ratchet geared instruments of the eighteenth and nineteenth centuries.

PHILIP F. WILLIAMS.

This proposed course, *A Curriculum for Schools of Medical Technology*,¹⁹ arranged by Dr. Israel Davidsohn in a loose-leaf folder, is an outline for instruction for medical technologists. It is not a textbook but contains a list of procedures and shows where source material may be obtained. The textbooks and monographs which are recommended are standard, and should be found in most hospital libraries. The suggestion for instruction for technicians covers eight chapters, and can be regarded as being exceptionally complete. The curriculum has been recommended by The American Society of Clinical Pathologists and should be of advantage to hospitals which are organizing instruction in this auxiliary branch of pathology as well as to those physicians in charge of teaching clinical pathology in medical schools.

PHILIP F. WILLIAMS.

Encouraged by the late Colonel Fielding H. Garrison, Dr. Solomon R. Kagan has added to his previously published medicohistorical studies a new small volume, entitled, *Leaders of Medicine*.²⁰ It contains bibliographic sketches of the following twelve outstanding American and European physicians: Henle, Virchow, Weir Mitchell, Jacobi, Albutt, Solis-Cohen, Billings, Cohnheim, Weigert, Osler, Welch and Ehrlich.

Though concise in form these biographies present not only competent surveys of their respective contributions to medical advance but as well clear pictures of personal characteristics and traits. The physicians of the present generation are familiar with the names and the work of these twelve eminent scientists and will not fail to appreciate this opportunity of becoming acquainted with certain significant details of their lives.

HUGO EHRENFEST.

*The Bond Between Us—The Third Component*²¹ is a mixture of autobiographical, anecdotal and semiphilosophical ramblings of a very talented writer. It deals with the ill definable sympathy and bond which spring up unsought and spontaneously between individuals. The writer has led a very interesting and adventurous life, including experiences in mining in Alaska, a resident in Peterson's gynecologic and

¹⁸*The History and Evolution of Surgical Instruments.* By Dr. C. J. S. Thompson. Foreword by Dr. Chauncey D. Leake. 115 illustrations, 113 pages. Schuman's, New York, 1942.

¹⁹*A Curriculum for Schools of Medical Technology.* By Israel Davidsohn, M.D., Director of Laboratories and Pathologist, Mt. Sinai Hospital, Chicago, Illinois. 43 pages. Second Edition Revised. 1942.

²⁰*Leaders of Medicine. Biographical Sketches of Outstanding American and European Physicians.* By Solomon R. Kagan, M.D. 176 pages, and four illustrations. The Medico-Historical Press, Boston, Mass., 1941.

²¹*The Bond Between Us. The Third Component.* By Frederic Loomis, M.D. 267 pages. Alfred A. Knopf, New York, 1942.

Department of Reviews and Abstracts

Selected Abstracts

Gonorrhea

East, E. N.: Gonorrhea in the Female, *Canad. M. A. J.* 45: 250, 1941.

Six hundred and twenty-six cases of gonorrhea were found in 1,712 women presenting themselves to the Vancouver Venereal Disease Control Clinic. Diagnosis was based on smear and culture. *Trichomonas* infections were present in 20 per cent of the cases. Rectal gonorrhea was diagnosed in only 8 cases. Sixty-four per cent were cured on sulfanilamide therapy alone. Pelvic complications were present in 9.2 per cent of the cases. Final cure was based on smear and culture examinations one month after apparent clinical cure.

CARL P. HUBER

Hesseltine, H. Close, Mac, Lucile R., Adair, Fred L., and Hibbs, Donald K.: Preliminary Report of Sulfanilamide, Sulfapyridine, and Local Therapy in Gonococcal Infection in Women, *Am. J. Syph., Gonor. & Ven. Dis.* 25: 454, 1941.

Of 41 patients on local treatment, 8 (20 per cent) were cured and 33 (80 per cent) were not cured. Seventeen of the failures were shifted to chemotherapy, to which 16 responded; the 1 failure gave evidence of reinfection.

Of the 46 patients on sulfanilamide therapy, 32 (70 per cent) were cured and 14 (30 per cent) were not cured. Of the 14 not cured, 6 (43 per cent) showed evidence of reinfection; 8 (57 per cent) showed no evidence of reinfection; the probable drug failure was 17 per cent for this series.

Of the 63 patients on sulfapyridine, 45 (71 per cent) were cured and 18 (29 per cent) were not cured. Of the 18 not cured, 14 (77 per cent) showed evidence of reinfection; 4 showed no evidence of reinfection; the probable drug failure was 6 per cent for this series.

Chemotherapy is superior to local measures in the treatment of gonococcal infection in women.

With sulfapyridine therapy in gonococcal infection of women, the duration of treatment is shorter, the dosage is smaller, the response is quicker, the percentage of failures is lower, and the patient complains less of toxic symptoms than with sulfanilamide.

C. O. MALAND

Brundu, Carlo: A Brief Note About Sulfonamide Therapy and Gonosulfonamides in Blenorrhagic Infections, Especially in the Female, *Rassegna d'ostet. e ginec.* 48: 394, 1939.

The author presents and discusses a new sulfonamide preparation. It is a combination of methylene blue and sulfonamide. It is said to be a valuable addition to the armamentarium in antibleorrhagic therapy.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MAY 12, 1942

The following papers were presented:

Experience With the Latzko Extraperitoneal Caesarean Section at the French Hospital. Hervey C. Williamson, M.D., and Myron E. Goldblatt (by invitation).

The Treatment of Acute Inflammatory Masses of Tubal Origin by Iontophoresis With Acetyl Beta Methyl Choline Chloride, a Report of 94 Cases. Robert L. Craig, M.D., and Harry Kraff, M.D. (by invitation). (For original article, see page 96.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 7, 1942

The following papers were presented:

Some Unconscious Determinants in a Patient With Hyperemesis Gravidarum. Eli Marcovitz, M.D. (by invitation).

Puerperal Sepsis: An Analysis of Deaths in Philadelphia for Ten Years. Clarence C. Briscoe, M.D. (For original article, see page 144.)

Application of the New Classification of the Toxemias of Pregnancy to Three Hundred and Eighteen Fatal Cases. Philip F. Williams, M.D., and Edward Weiss, M.D. (by invitation). (For original article, see page 2.)

Presidential Address. Thaddeus L. Montgomery, M.D.

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MAY 1, 1942

The following papers were presented:

The Prevention of Mortality in Rupture of the Uterus. Charles A. Gordon, M.D., and Alexander H. Rosenthal, M.D.

Choice of Cesarean Section; the Advantages and Disadvantages of the Various Types. James P. Marr, M.D. (by invitation).

Forty-one infected children who were given no treatment of any sort were used as controls. It became apparent that the disease can undergo what may be called a "spontaneous cure." Of these children 87 per cent became and remained negative within twenty-eight weeks of observation, which gives a new concept of the natural course of gonorrhea in girls.

Among these 381 infected children, many of them very young or mentally deficient, not one instance of secondary infection of the conjunctiva was observed. Though 45 per cent of the treated and untreated children had positive rectal cultures, none developed a proctitis. Estrogenic treatment did not influence the rectal infection. However, in every case in which a sulfonamide was effective in the vaginal infection, it also cleared up the rectal infection.

Episodes of acute lower abdominal pain occurred in about 5 per cent during the acute stage of the vaginitis, presumably as a result of the extension of the infection. Gonococcal arthritis occurred rarely.

Estrogenic substances, applied orally or locally, led to clinical improvement but did not shorten the persistence of positive cultures.

Sulfanilamide was effective in 43 per cent of 53 cases, producing prompt clinical and bacteriologic cure. Sulfapyridine and sulfathiazole proved even superior, yielding 87 per cent cures in 77 patients. The response is dramatic, smears and cultures become negative within twenty-four hours. The most satisfactory administration was a dosage of $1\frac{1}{2}$ grain of sulfathiazole per pound of body weight, limited to 30 grains a day, in 3 to 6 doses, given for 7 days.

HUGO EHRENFEST

Sulkin, S. Edward, and Gottlieb, Eleonore: The Use of an Improved Culture Medium in the Diagnosis of Gonococcal Infection in the Adult Female, *Am. J. Syph., Gonorr. & Ven. Dis.* 25: 22, 1941.

1. A total of 2,050 examinations for the diagnosis of gonococcal infection in the adult female were made, using culture and smear method simultaneously.

2. Approximately twice as many cases of gonorrhea were detected by the cultural method as by the smear method. In many instances the gonococcus was isolated from the treated cases in which repeated microscopic examination was negative.

3. The cultural method aids in establishing a diagnosis in cases presenting doubtful microscopic findings.

4. Since positive smears may be associated with negative cultural findings, the best procedure for the laboratory diagnosis of gonorrhea should include use of cultural as well as the smear method.

5. Proteose-peptone No. 3, hemoglobin agar (Difco), is an excellent medium for use in the diagnosis of gonorrhea.

C. O. MALAND

Carpenter, Charles M.: The Cultural Method for the Diagnosis of Gonococcal Infection, *Puerto Rico J. Publ. Health* 15: 197, 1940.

A review of the literature on the use of the cultural method for the diagnosis of gonococcal infection, since its introduction into this country, disclosed an unanimity of opinion on the striking superiority of the procedure over the "smear" method.

It is recognized, however, that the present method has limitations, is a somewhat complex procedure and should never be used to the exclusion of smears, but that both procedures should be employed. In cases of acute anterior urethritis, smears alone are usually adequate; on the other hand, the treatment of gonococcal infections with sulfanilamide or similar compounds has increased the necessity of employing cultures, because patients may become carriers of the gonococcus after apparent clinical cure. It is important, therefore, that practitioners be trained to consider

The formula of the tablet is given as: para-aminophenylsulfamide gr. 0.40; hexamethylenetetramine anhydromethylene citrate gr. 0.30; methylene blue gr. 0.05 and an excipient quantity sufficient. The treatment consisted of a gradually increasing dosage from one tablet the first day to a maintenance level of six tablets daily. The maintenance dosage was given for a period of ten to twenty days following which the dosage was gradually diminished to a single tablet prior to cessation of treatment. A few more resistant cases required treatment for a period of fifty to sixty days.

In the female patients this treatment was supplemented with daily local therapy for the first fifteen days: potassium permanganate, protargol, glycerin tannate tampons alternated with ichthyol tampons.

The author reports a 1 per cent drug intolerance to this therapy. Sixty-three women and forty-five men were treated. The conclusions state that the aforementioned therapy, when combined with local treatment, reduces considerably the time interval required for successful cures, and at the same time the possibilities of further complications are definitely limited. Specific percentages regarding the number of successful cures are not given, although the author states it includes "the majority." He summarizes further that while the local condition is cleared usually in ten days there may be a persistence of gonococci in the secretions for a period of ten to fifty days in some cases.

CLAIR E. FOLSOME

Cohn, Alfred, Steer, Arthur, and Adler, Eleanor L.: Further Observations on Gonococcal Vulvovaginitis, *Am. J. Syph., Gonor. & Ven. Dis.* 25: 329, 1941.

The authors' summary is as follows:

1. Cultures are superior to smears for diagnosis and determination of cure.
2. Untreated cases undergo spontaneous cure within thirteen weeks in over 50 per cent of patients.
3. About one-fifth of these patients develop the carrier state, in which occasional positive cultures occur in the absence of clinical signs even after twenty-eight weeks of observation. However, all patients ultimately become negative.
4. Sulfanilamide therapy results in cure in two-thirds of the hospitalized patients within two weeks of treatment.
5. Sulfapyridine was followed promptly by negative cultures in all cases with recurrence in less than 10 per cent.
6. Estrogenic substance brought about early clinical improvement, but it appeared that the course of the disease was little different from that in the controls.
7. Rectal infections were diagnosed by the finding of positive rectal cultures in 45 per cent of the patients. In none was there characteristic evidence of gonococcal proctitis clinically.
8. Contact with a source of infection, either child or adult, must be intimate before the disease can be transferred.

C. O. MALAND

Cohn, Alfred, Steer, Arthur, and Adler, Eleanor L.: New Concepts of Gonococcal Vaginitis, *J. Pediat.* 20: 41, 1942.

False diagnosis of gonorrheal vaginitis can be avoided only by smear and culture, the latter being by far more reliable. Thus in a total of 1,715 patients, who were studied because they had symptoms or were contacts of infected persons, only 381 girls were found to have gonorrhea, an incidence much lower than usually expected.

No patient was considered infected unless she had at least one positive culture and none cured unless there were at least seven consecutive negative smears and cultures during a period of at least sixteen weeks.

On the basis of a limited experience, it does not appear that the menstrual cycle plays any definite role in determining the incidence of culture positivity in untreated chronic gonorrhea of women.

In 3 of 56 cases, the urethral culture was positive for the gonococcus while the cervical secretions of these patients did not reveal the organism. In 53 of the 56 women, the cervical secretions were found by the culture method to contain gonococci, but cultures of the urethral secretions demonstrated the gonococcus in only 23 instances.

Combining the urethral and cervical secretions in a single carrying tube is recommended for further study as a feasible and economical means of employing the culture method in gonococcal infections in women. It is suggested that the inclusion of Nile blue in the medium may enhance the value of this method.

In the face of clinical and epidemiologic evidence of chronic gonococcal infection in women, it may be unwise to withhold treatment solely on the basis of negative culture results.

C. O. MALAND

Newborn

Bloxsum, Allan: The Difficulty in Beginning Respiration Seen in Infants Delivered by Cesarean Section, *J. Pediat.* 20: 215, 1942.

In a careful analysis of 100 cesarean babies, the writer found that 42 required active resuscitation, against only 18 in 100 normal deliveries.

The role played in apnea by analgesia, surgical anesthesia usually with premedication, and such conditions as toxemia, placenta previa or premature placental detachment indicating the operation, are appreciated. But the author stresses other factors which in the cesarean baby probably interfere with prompt initiation of normal respiration.

There is absence of respiratory effect on the fetus exerted by alternating pressure and release of pressure as result of uterine contractions during labor. During a contraction, compression of the placenta forces more oxygen-carrying blood into the fetus. Thus an accumulating oxygen deficiency might impair the ability of the fetal respiratory center for prompt response after delivery. In cesarean section there also is missing the compression of chest and lungs within the birth canal which in vaginal delivery may be of significance for the first inspiration.

HUGO EHRENFEST

Baird, Dugald, and Wyper, John F. B.: High Stillbirth and Neonatal Mortalities, *Lancet* 2: 657, 1941.

The causes of stillbirth and neonatal deaths in the Aberdeen Maternity Hospital were analyzed. In 3,427 booked cases where the baby was full term there was no adequate explanation of the death in 25.3 per cent of the total; trauma accounted for 18.9 per cent and fetal deformity for 8.3 per cent. There were few deaths from infection in hospital.

Among the premature births no adequate explanation of the reason for the premature onset of labor could be found in 37 per cent; toxemia accounted for 15.2 per cent. The death rate was largely determined by the degree of prematurity.

The combined stillbirths and neonatal deaths in private specialist practice, in hospital practice and domiciliary practice were found to be 12 per 1,000, 54.5 per 1,000, and 78.5 per 1,000. The low figure in the first group is probably due to a combination of favorable factors, economic, nursing, and medical. In the second group the nursing and medical factors are favorable but economic conditions are unfavorable. In the third group the high figure indicates the need for an all-round improvement in medical and nursing care as well as economic conditions.

There is thus a large wastage of child life (approximately 80 per 1,000 births) associated with childbirth in Scotland, intimately connected with unfavorable

the cultural method as an essential in the diagnosis of gonococcal infections and should carefully train technicians in the routine work. The technique is given for obtaining specimens, making cultures, identifying the gonococcus and interpreting the results.

J. P. GREENHILL

Russ, Joseph D., and Collins, Conrad G.: *The Treatment of Prepubertal Vulvovaginitis With a New Synthetic Estrogen*, J. A. M. A. 114: 2446, 1940.

The authors treated 25 cases of gonorrheal vulvovaginitis with diethylstilbestrol. One milligram was given three times daily until twenty were given. The tablet was crushed and placed in two ounces of milk. In 22 cases negative smears for pus and gonococci were obtained at the end of seven days' treatment. Two cases required nine and eighteen days of treatment, respectively. Within seventy-two to ninety-six hours the discharge changes in character becoming thin and mucoid and white. Complete disappearance of any type of discharge is noted within one or two weeks after discontinuance of the treatment. No vomiting was noted when the stilbestrol was administered in milk. In approximately two-thirds of the cases, a darkening of the nipple and areola occurred together with a painless enlargement of the breasts. Only two cases have had recurrences and were retreated with 20 mg. of stilbestrol with negative smears at the end of seven days.

WILLIAM BERMAN

Mahoney, J. F., Wolcott, R. R., and Van Slyke, C. J.: *Sulfamethylthiazole and Sulfathiazole Therapy of Gonococcal Infections*, Am. J. Syph., Gonorr. & Ven. Dis. 24: 613, 1940.

1. Experiences with the use of sulfamethylthiazole in the treatment of 136 cases of gonococcal infection have been recorded. The cure rate was 92.1 per cent in the previously untreated patients but was lowered to 53.8 per cent in the group which had failed to be cured by earlier chemotherapy.

2. Because of the production of peripheral neuritis the use of sulfamethylthiazole is not advised for the treatment of gonococcal infections.

3. Sulfathiazole was employed in the treatment of 106 male patients. In 79 completed cases the cure rate was 91.1 per cent. The group which had previously failed to be cured by chemotherapy did not have a lowered cure rate.

4. Evidences of toxicity attributable to sulfathiazole were negligible.

5. Ingestion of larger amounts of the drug did not influence the cure rate or the incidence of toxic responses.

6. The inference seems to be permissible that sulfathiazole constitutes an effective addition to the therapy of gonorrhea.

C. O. MALAND

Mahoney, J. F., Van Slyke, C. J., Wolcott, R. R., Thayer, J. Durward, and Nimelman, Anna: *Culture Studies in Chronic Gonorrhea of Women*, Am. J. Syph., Gonorr. & Ven. Dis. 26: 38, 1942.

Approximately only 21 per cent of 2,429 prostitutes were shown by a single culture examination to harbor the gonococcus in the cervical secretions.

Prolonged cultural investigations of untreated gonorrhea in women showed that many of these patients reverted to cultural negativity, a status which was maintained throughout the period of observation or marked by one or more gonococci-positive cultures occurring sporadically after a relatively long series of negative cultures. In almost all instances there was no apparent tendency for clinical evidence of the disease to disappear.

is unimpaired by narcotics and anesthetics (possible traumatic effect of birth is not mentioned by the writer) breathing begins at once.

Rhythms of shallow and rapid respiratory movements, occasionally observed late in gestation, signify temporary increase of excitability of the respiratory center, or an elevation of blood carbon. Such fetal respiratory movements should give cause for apprehensiveness. Under normal conditions the fetus receives from the blood well saturated with oxygen, it is shunted through the fetal heart directly to the brain so that anoxemia of the center is avoided.

Aspiration of amniotic fluid is not a normal phenomenon. It occurs only under conditions of marked anoxemia.

HUGO EHRENFEST

Esch, P.: *Genesis of Icterus Neonatorum*, Zentralbl. f. Gynäk. 65: 574, 1941.

The author studied the blood changes in the newborn infant and concludes that icterus neonatorum is in great part hemolytic in origin. At birth the large number of erythrocytes present is progressively decreased as the lungs develop their full function. Hemolysis of many cells leaves much blood pigment available to the liver for conversion to bile pigment. The author postulates a special permeability of lining membranes and epithelial tissues to the pigments at this time in the infant with the clinical symptom of jaundice resulting.

R. J. WEISSMAN

Willumsen, H. C., Stadler, H. E., and Owen, C. A.: *Comparative Effect of Vitamin K and Whole Blood on Prothrombin Deficiency of New-Born Infant*, Proc. Soc. Exper. Biol. & Med. 47: 116, 1941.

Vitamin K given orally or parenterally causes a rapid rise in the plasma prothrombin level of newborn infants with hypoprothrombinemia whether there is a hemorrhagic tendency or no clinical manifestation of the depressed prothrombin level. Whole blood has a slight additive effect when injected intravenously. Satisfactory treatment with adequate blood transfusions (30 to 50 c.c.) has the disadvantage of requiring such specialized technical proficiency that it is frequently not available when needed. Moreover, some time is lost by the need for cross-matching. Injections of blood, other than intravenously, have no effect on the clotting time within twelve to fifteen hours as measured by plasma prothrombin level.

WILLIAM BERMAN

Paige, B. H., Cowen, D., and Wolf, A.: *Toxoplasmic Encephalomyelitis; Further Observations of Infantile Toxoplasmosis; Intrauterine Inception of the Disease; Visceral Manifestations*, Am. J. Dis. Child. 63: 474, 1942.

Three additional cases of infantile toxoplasmic encephalomyelitis are presented. In addition a fourth case, previously diagnosed as acquired internal hydrocephalus is reclassified in the above syndrome. This raises the number of definitely identified cases to nine. The article contains an excellent discussion of the literature and presents additional evidence toward the intrauterine onset of the disease. Failure to find evidence of toxoplasmic infestation in either the mother or placenta admittedly weakens this point of view and leads the authors to suggest a possible vaginal route of infection.

L. M. HELLMAN

Berlind, M.: *Fetal Shock—Treatment With Desoxycorticosterone Acetate*, Canad. M. A. J. 45: 534, 1941.

A preliminary report is presented of the treatment of fetal shock with desoxycorticosterone acetate plus saline infusions. The author defines such shock as the "state of the newborn which immediately after delivery, usually difficult, is that of

economic conditions, and malnutrition and fatigue in the mother. If investigations on a large scale substantiate these findings, then measures to ensure proper feeding and care of pregnant women are urgently needed.

CARL P. HUBER

Chuniard, E. G., Osgood, E. E., and Ellis, D. M.: Hematologic Standards for Healthy Newborn Infants, *Am. J. Dis. Child.* 62: 1188, 1941.

A study of oxalated fontanel blood of 195 infants, 20 of them less than ten days old, yielded the following results:

Average erythrocyte count 4,600,000 (extreme ranges 2,600,000 and 6,300,000). Average hemoglobin concentration 16.3 Gm. per 100 c.c. (extreme ranges 10.3 and 22.6 Gm.). Average packed red cell volume 43.4 c.c. per 100 c.c. of blood (extreme ranges 25.5 and 61.0 c.c.). Average hemoglobin coefficient 17.8 (extreme ranges 12.5 and 23.5). This corresponds to an average color index of 1.00 (extreme ranges 0.78 and 1.23). Average volume coefficient 47.6 (extreme ranges 34 and 61). Average saturation index 1.00 (extreme ranges 0.77 and 1.460).

The cells of newborn infants are larger and contain more hemoglobin than those of older persons but the corpuscular hemoglobin concentration is similar to that of adults. Hemoglobin contents should be reported in terms of grams.

HUGO EHRENFEST

Hogblom, G.: The Question of So-called Giant Babies With Report of Two Cases, *Acta obst. et gynec. Scandinav.* 21: 79, 1941.

Among 40,395 deliveries in the Upsala Women's Clinic, there were 94 cases of giant babies, an incidence of 0.23 per cent. By a giant baby the author implies a baby weighing 5,000 Gm. or more. An analysis of the 94 cases revealed that these babies occurred generally in multiparous women between 30 to 34 years of age, that pregnancy was usually prolonged, that most deliveries were spontaneous and within twenty-four hours, that most of these babies presented by the face, that there were no extensive perineal lacerations, that the third stage of labor was normal, that the majority of the babies were males, that the mortality for the mothers was zero and that four babies were stillborn and four died after delivery.

J. P. GREENHILL

Windle, Wm. F.: Physiology and Anatomy of the Respiratory System in the Fetus and Newborn Infant, *J. Pediat.* 19: 437, 1941.

Based on an analysis of extant literature and an extensive experimental study on various types of pregnant animals the author offers a summary of his conclusions.

It is becoming evident that the physiology of respiration in utero is not greatly different from that of the newborn infant or even of the adult individual. Early in embryonic life begins development of the part of the motor system which is later to be concerned with breathing. Soon higher neurons are formed and are brought into a mutually integrated aggregates a respiratory center connected with the somatic motor system. This can be brought into premature activity by carbon dioxide acting upon it directly, or by anoxia elevation of its excitability. It is doubtful whether this respiratory mechanism actually functions in the normal course of intrauterine existence. It seems a dormant system charged with potentialities long before it is of any actual use. Premature birth finds the new individual well prepared in respect to its respiratory system.

Under experimental conditions it is very easy to start respiratory movements of the fetus. Respiration begins at birth because excitability of the center increases as anoxemia builds up during placental separation. If excitability of the center

hypoprothrombinemia develops in the first three days of life. Infants with hemorrhagic disease of the newborn show a markedly prolonged prothrombin time; premature infants show a moderately prolonged prothrombin time.

Nine babies suffering from asphyxia of the newborn showed marked prolongation of the prothrombin time. Three of these infants were bleeders. Anoxemia may be a factor in the production of hypoprothrombinemia in this condition. There is no relationship between physiological jaundice of the newborn and hypoprothrombinemia.

Vitamin K administered orally or intramuscularly controlled the spontaneous bleeding in a group of 8 infants with hypoprothrombinemia. In the light of the reported findings a prophylactic dose of vitamin K might be of value in premature infants and in those suffering from asphyxia of the newborn. The use of vitamin K is indicated in cases of traumatic bleeding, especially intracranial hemorrhage.

The administration of vitamin K is advisable before all operative procedures in the first week of life.

CARL P. HUBER

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2:00 P.M.

Arrangements will be made so far as possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 13, 1943, Part I examination, who are entering military service, or who are now in service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding the records to the Office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in service, eligible for Board examination, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

The Part II examination will be held at Pittsburgh, Pennsylvania, from May 19-25, 1943. Notice of the exact time and place of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations applying to civilian candidates.

Applications are now being received for the 1944 examinations of the Board.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

a living limp traumatized infant'' with diminished muscular tone, pale grayish color, and difficult respiration following resuscitation. Twelve such newborn infants were treated with desoxycorticosterone acetate in doses varying from 0.1 c.c. to 0.5 c.c. daily with 50 to 100 c.c. normal saline subcutaneously daily. All survived. Three of the infants had been delivered spontaneously, 5 by forceps, 4 by breech extraction and 1 by cesarean section.

CARL P. HUBER

Rouhunkoski, M., and Saksela, N.: Hypoprothrombinemia Neonatorum and Its Relationship to Vitamin K, *Acta. obst. et gynec. Scandinav.* 112: 203, 1941.

The authors found that in mature children the average prothrombinemia period was fifty seconds during the first hours post partum and that the time increased suddenly to 96 seconds on the second day of life. The prothrombinemia period increased still more on the third and fourth day after which there was a gradual decrease. Prothrombin periods in premature babies was shorter than in full-term children. It is possible to almost entirely prevent the physiologic decrease in the prothrombin content of fetal blood by giving vitamin K to the mothers from fifty to sixty minutes before delivery or to the infants immediately after birth.

J. P. GREENHILL

Wespi, H. J.: Prophylaxis of Goiter in the New Born, *Schweiz. med. Wehnschr.* 70: 925, 1940.

According to Wespi iodine prophylaxis in the form of iodized salt was introduced in 1922 in a certain region in Switzerland where goiter was endemic and 50 per cent of the newborn infants had enlarged thyroids. This prophylactic measure greatly reduced the incidence of goiter in the newborn infants but did not bring about its complete disappearance. Eggenberger therefore introduced additional individual prophylaxis in pregnant women. They were given a stock mixture which increased the iodine content of the salt used in their household three to four times that of ordinary iodized salt. These measures resulted in reduction of incidence of struma in the newborn infants to 5.3 per cent. The iodine provided in iodized salt may not be adequate for pregnant women obliged to restrict their salt intake to avoid toxiosis. In such cases medication with potassium iodide can be resorted to. Wespi emphasizes that the reduction in incidence of goiter is dependent on the quantity of iodine given in addition to that provided by the food. If during the last weeks of pregnancy the daily addition amounts to approximately 150 micrograms of potassium iodide, no measurable enlargement of the thyroid is evident in the nursling. If this quantity of iodine is administered during the last three months of pregnancy, enlargement of the thyroid is not even perceptible. Unequivocal results of prophylaxis and knowledge of the quantities of iodine ingested in regions where goiter is not endemic corroborate the correctness of the theory of iodine deficiency in goiter. Since the present degree of iodization of cooking salt does not always prevent struma in the newborn infant, it should be increased so that each kilogram of salt contains at least 10 mg. potassium iodide. This form of prophylaxis involves no danger since the small physiologic quantities of iodine do not cause existing strumas to become toxic.

J. P. GREENHILL

Ross, S. C., and Malloy, H. T.: Blood Prothrombin in the Newborn: The Effect of Vitamin K Upon the Blood Prothrombin and Upon Hemorrhagic Disease of the Newborn, *Canad. M. A. J.* 45: 417, 1941.

A study of 113 untreated and 93 vitamin K treated infants confirms previous reports. A cord blood at birth shows a normal prothrombin time and a temporary

- Pacific Coast Obstetrical and Gynecological Society.** *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, San Francisco, Calif., November, 1942.
- Washington Gynecological Society.** *President*, John Warner. *Secretary*, L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Norman F. Miller. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** *President*, Ralph Hoffman. *Secretary*, Purvis L. Martin, 2001 Fourth Ave., San Diego, Cal. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** *President*, J. H. Fjelda. *Secretary*, Ralph E. Leigh, 111 North Fifth St., Grand Forks, N. D.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting, Hershey, Pa., May 30, 31, June 1, 1943.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, September, 1943.
- Central Association of Obstetricians and Gynecologists.** *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. (Undecided.)
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Next meeting, February, 1943, Southern Pines, N. C. (Cancelled.)
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting. (Cancelled.)
- New York Obstetrical Society.** *President*, Henry T. Burns, *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, John C. Hirst. *Secretary*, James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Edward Allen. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, Samuel Lubin. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Lawrence Warton. *Secretary-Treasurer*, John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, J. L. Gilmore. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** *President*, Frank A. Pember-ton. *Secretary*, A. F. G. Egelow, 31 Maple Street, Springfield, Mass. Meetings held in May and December.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

and it may even be that a baby is cyanotic at birth because it is mentally deficient," rather than mentally deficient because it was cyanotic.

In studies like those under discussion, it is almost impossible to provide adequate physiologic controls; especially is this true because single births are the rule in man. Here the physician must turn to the laboratory.

We have put Schreiber's thesis to a laboratory test and the results prove conclusively that anoxia at birth can produce permanent degeneration changes in the brain. We shall summarize our observations in the present report and deal more completely with certain aspects of this problem in later publications when more experiments will have been completed.

Material and Procedures

The guinea pig was chosen for several reasons. Estrus occurs throughout the year at intervals of about fifteen days. Usually two or three relatively large (90 Gm.) and mature young are born after a gestation period of about sixty-seven days. Placentation is of the highest type, more comparable with that in man than some of the other laboratory animals. Survival time during anoxia is much shorter in the guinea pig than in other animals. In this respect the guinea pig may resemble the newborn human infant, but it is well known that it is more advanced in development at birth.

The experiments to be described fall into two groups, although the methods of inducing anoxia were the same in all. After infiltrating the abdomen with 1 c.c. of a 1 per cent solution of procaine hydrochloride, the uterus was obtained through a midline incision, and one fetus was delivered immediately to serve as a control for comparison with the litter mates which were to be subjected to anoxia. The uterine vessels were then occluded with a stomach clamp or small incisions were made in the uterus and the umbilical cords of the other fetuses were caught with artery forceps and clamped. Thus anoxemia was induced in the fetuses for periods of various lengths.

Fifty-eight animals were delivered as soon as the intrauterine respiratory movements, which were brought on by the anoxemia, became weak or had ceased. Resuscitation was attempted by mechanical stimulation, electrical stimulation, and injection of respiratory stimulants in the fetuses which had become apneic. These efforts were ineffectual, for only the specimens delivered before anoxial apnea was established survived.

Forty-five other animals were delivered after all intrauterine respiratory efforts had ceased. Resuscitation was delayed until the fetal heart had become slow and weak, often after it had become too feeble to palpate. Resuscitation was accomplished by inflating the lungs gently with oxygen or oxygen containing 10 per cent carbon dioxide. The gas was contained in a small rubber bag attached to a hypodermic needle of small bore (No. 25). The needle was inserted into the trachea through the neck and rhythmical inspirations and expirations were simulated by compressing and releasing the trachea distal to the needle.

Ninety guinea pigs, litter mates of the 103 experimental specimens, served as controls in studying the effects of anoxia. In addition, 16 others were delivered by cesarean section and 26 were allowed to be

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Original Communications

ASPHYXIA NEONATORUM*

An Experimental Study in the Guinea Pig

W. F. WINDLE, M.S., PH.D., AND R. F. BECKER, M.S., PH.D.,
CHICAGO, ILL.

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IT HAS been recognized in recent years that high incidence of stillbirths and neonatal deaths is associated in part with neonatal asphyxia.¹ Of equally great concern is the observation that prolonged anoxia in the newborn infant may cause cerebral injury and lead to clinical neurologic manifestations with impairment of the intellect. Brain pathology resulting from anoxia in the adult has been described by many investigators.¹⁻⁵ A similar relationship between neonatal anoxia and cerebral damage has been reported.⁶⁻⁸

In a series of 500 patients seen at various ages because of cerebral symptoms, Schreiber⁵ found about 70 per cent of those whose birth records were available had histories of apnea. Schreiber and others have studied the relationship between the incidence of respiratory difficulties at birth and the use of analgesics and anesthetics during labor.

The theory that fetal anoxemia resulting from narcosis during delivery may produce permanent degenerative changes in the brain of the infant is a challenge to the obstetrician; however, results of clinical studies have not been completely accepted because, as Galloway⁹ pointed out in discussing Schreiber's paper, the human material was selected and lacked adequate controls. He holds that "since the world began, about 2 per cent of the population has been born defective mentally.

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The period of survival of respiratory movements after occluding the circulation bore a relationship to the total volume of oxygen-laden blood available to the fetuses. This was demonstrated by comparing the duration of respiratory movements in utero after clamping the uterine vessels (i.e., when the oxygen of all the fetal blood was available) with that after clamping the umbilical cords (i.e., when the blood of the fetal body but not that in the placenta was available). In 42 fetuses with the uterine vessels occluded, the average duration of the respiratory efforts was six minutes and twenty-four seconds (range ten minutes, thirty seconds to four minutes, twenty-four seconds). In 28 fetuses whose umbilical cords were clamped, the respiratory movements persisted five minutes and 41.5 seconds (range 8 minutes to 3 minutes, 20 seconds). The blood in the placental circuit, therefore, contained on the average enough oxygen to prolong respiratory efforts for 42.5 seconds. It would appear from this that the placental circuit contains a little more than 11 per cent of the total fetal blood at full term. This is a considerably smaller proportion of the fetal blood than is in the human placenta, but we do not know how much was static in the guinea pig placenta and unavailable to the fetus.¹²

In several experiments after all respiratory movements had ceased in utero, a gasp or two were initiated in the cyanotic newborn animals by compressing the placenta and forcing placental blood through the umbilical veins into the fetus before clamping the cord. A little extra oxygen is assumed to have been supplied to the fetal brain from the placental blood. This is a point worth considering when asphyxia livida is encountered.

Immediate Cardiovascular Effects of Anoxia.—The heart rate of the full-term guinea pig was determined by palpating the intact maternal abdomen or the intact uterus immediately after opening the locally anesthetized abdomen. It varied between 120 and 260 per minute, with a mean of 164 per minute in the intact abdomen and 181 per minute in the intact uterus after opening the abdomen. The slight increase in heart rate occurred because the uterus was handled and became more tonic. It may be interpreted as the initial effect of anoxemia. After clamping the uterine or umbilical vessels the heart slowed to about half its normal rate in two minutes or less. This we believe to be a direct anoxial effect.¹³ Re-establishment of circulation caused an immediate return to nearly the previous rate. With prolongation of the anoxia, the heart became slower and weaker, averaging 52 beats per minute, before artificial respiration was begun. The slowest rate we could count was 24 per minute. The heart could be palpated in most fetuses for twelve to fifteen minutes. Effective heart action continued two to three times as long as the intrauterine respiratory efforts. In several very large, possibly postmature fetuses weighing 145 to 165 Gm., the heart failed more quickly, suggesting correlation between size or maturity of the animal and period of survival of heart action during anoxia.

born normally. These 42 specimens were used to study normal behavior in the neonatal period and normal accomplishments in the learning tests, providing additional controls for the investigation.

The behavior of the resuscitated animals and their litter mates was observed at frequent intervals during the first few days of life, or until recovery from the effects of anoxia appeared to be complete. The experimental animals often required special care and feeding for several days. After all observations and tests had been completed, the experimental and control guinea pigs were anesthetized and perfused with 10 per cent formalin. Autopsies were performed and the brains and other tissues were preserved for histologic study.

Results

Immediate Respiratory Effects of Anoxia.—During the last few days of the gestation period, the nonnarcotized guinea pig fetus is adequately supplied with oxygenated blood from the placenta and is apneic. This fact was established by experiments reported previously.¹⁰ Critical examination of evidence fails to support the prevalent belief that the fetus normally executes rhythmical respiratory movements and aspirates its amniotic fluid in utero.¹¹ The lungs of the full-term fetus are in a state of initial atelectasis in which there is only about 2 per cent pulmonary space.¹⁰ When aspiration was deliberately induced by asphyxiation, the pulmonary space increased to 16 per cent, and after an hour of breathing air, 40 per cent.

In the present experiments, the uterus was incised promptly after opening the locally anesthetized abdomen, and the control specimens were delivered before they could gasp and aspirate amniotic fluid. Although apneic in utero, they breathed immediately at delivery. The promptness with which the first breath of air was taken when the head was freed from the fetal membranes suggested that factors other than impairment of the placental circulation helped induce breathing. Delivery of the fetal nose alone led to the first breath in five to thirty seconds (often less). It is probable that as the environment changed new afferent impulses affected the threshold of the young respiratory center and enhanced the effects of beginning anoxemia.

Clamping the uterine or umbilical vessels invariably induced intra-uterine respiratory movements as well as other somatic and visceral activities in the experimental fetuses. Within a few seconds to two minutes, shallow, rapid, ineffectual respiratory-like efforts were often made in utero. These lasted only a few seconds but occurred at rates equivalent to 50 to 108 per minute. They were followed by brief periods of quiescence preceding long series of slow deep rhythmical respiratory movements, often of the dyspneic type, which began slowly, increased in rate and depth and then became very weak, although more rapid; they varied in rate between one and 14 per minute. These respiratory efforts resulted in aspiration of amniotic fluid, containing meconium which had been churned by the initial struggling and squirming of the fetuses when the clamps were applied to the vessels.

ployed. Twelve others, including 5 prematures, responded to the resuscitation but died before learning tests could be given them. Causes of death were (1) cyanosis and respiratory failure within a few hours (one developed pneumothorax); (2) pulmonary hemorrhages leading to death at eleven hours in one, and on the third day in another; (3) hemorrhagic lungs and stomach, bronchus plugged with meconium, and neural symptoms of complete spinal transection leading to death on the second day in one specimen; (4) unknown causes led to death on the fourth, sixth, and ninth days in three animals.

Resuscitation was ineffectual in 11 full-term and two premature fetuses. Inadequate time was given to it in four of these animals; accidents, such as pneumothorax and fracture of the trachea, occurred in four; and the bronchial tree had been plugged with aspirated meconium which prevented inflation of the lungs in one specimen. Anoxia was prolonged beyond the point of cardiac recovery in four of the animals including the three large, possible post-mature fetuses with unusually short survival times.

These results demonstrated the efficacy of positive inflation of the lungs with oxygen in the fetus whose respiratory center was temporarily paralyzed and somatic musculature was in a state of atonia. So long as effectual heart action persisted resuscitation of this type had a good chance of being successful. If we consider only the cases in which a true anoxic apnea with pallor, bradycardia and hypotonia existed, resuscitation was accomplished in 71 per cent; and most of the failures were due to faulty technique. On the other hand without positive lung inflation resuscitation was successful in not one instance. Those animals which survived did so because a true anoxic apnea had not been reached before the specimens were delivered. The urgency for quickly bringing oxygen to the blood in asphyxia pallida cannot be overstressed.

Effect of Anoxia on Body Weight.—Many of the newborn resuscitated guinea pigs lost more weight in the first three days of life than their litter mate controls. This was especially marked in those which exhibited marked persistent symptoms of brain damage. The weight averages for the entire series were lower for the resuscitated group than for their controls throughout the first four weeks of life. Guinea pigs born naturally, lost less weight immediately after birth and maintained higher average weights throughout the first four weeks than either the resuscitated animals or their litter mates. One explanation of this may be that all the animals delivered by hysterotomy were reared by foster mothers. Cole¹⁵ has pointed out that loss of blood in the placental circuit leads to abnormal weight loss, but we have not been able to confirm this in man.¹⁶

Cardiac Recovery After Anoxia.—Administration of oxygen or oxygen containing 10 per cent carbon dioxide led to recovery of the heart almost immediately. An increase in rate and strength of the beat could be detected after inflating the lungs two or three times in some of the animals. If this was not manifested within three minutes, the

Anoxia induced by clamping uterine or umbilical vessels produced the characteristic picture of asphyxia pallida; namely, apnea, bradycardia, atonia, relaxation of the anal sphincter and cold pale skin. The blood vessels in the skin were never dilated but those in the deep parts of the body were. Occasionally in the largest fetuses, the neck veins were engorged with blood. Usually, however, it was the vascular bed of the brain, viscera and placenta that appeared congested. This condition was often noted in those animals which failed to respond to resuscitation. It would seem that the fetuses bled into the visceral capillary beds in profound states of anoxia. Weber¹⁴ reported this in human infants.

Recovery and Survival of Controls and Experimental Animals.—Ninety guinea pigs were delivered without general anesthesia to serve as controls. Twelve were premature (63 to 65 days) and 78 were full-term births (66 to 67 days). Seventy-five of the full-term animals lived throughout the experimental period and the period of the learning tests, or were healthy young animals, killed, and preserved when their experimental litter mates died; only one of these showed any tendency to develop cyanosis in the neonatal period and this was transient. One full-term control animal died on the fourth day when its mother and litter mates likewise died of undetermined cause. Two full-term guinea pigs were runts, weighing only 41 and 53 Gm. Both developed cyanosis and died shortly after birth (one of them had a congenital atresia of the urethra with a distended bladder occupying more than one-half of the abdominal cavity).

Eleven of the 12 premature controls showed respiratory difficulties after birth and 10 of them died or were killed shortly after birth or within the first week. The relation of prematurity to cyanotic tendencies was thus strikingly demonstrated.

Fifty-eight guinea pigs were rendered anoxic only until intra-uterine respiratory movements ceased or had become very weak. (a) Eighteen, including one premature, recovered completely after manifesting various symptoms of anoxia and cyanosis. (b) Four survived a short time; two of these were premature births. The causes of death were determined to be the following: Two died in an hour or less because the lungs failed to fill adequately with air. One died on the fourth day of unknown cause. The other died on the seventh day in a fit of epileptiform convulsions. (c) Thirty-six, including 7 premature animals, failed to breathe after delivery, or they gave only one or two feeble gasps. Various techniques were tried to resuscitate them, including mechanical and electrical stimulation, injections of sodium cyanide, coramine and alpha lobeline solutions, without success. All were flaccid and pallid or cyanotic. We are certain that many if not all would have responded to oxygen had proper measures been taken to inflate the lungs with it.

Forty-five guinea pigs were subjected to anoxia for periods of six minutes to twenty-one minutes until the heartbeats became weak and slow or could no longer be felt. Twenty, including 3 prematures, recovered completely when resuscitation by positive inflation of the lungs with oxygen or oxygen containing 10 per cent carbon dioxide was em-

In several experiments with premature animals, it was observed that the control specimens tended to become cyanotic in the course of the first few hours although their asphyxiated litter mates, resuscitated by positive inflation of the lungs, had no difficulty. This may have been due to the forced opening of alveoli in the lungs of the latter.

Failure of the lungs to become opened by gentle inflation was observed in a few instances. This was due to aspiration of meconium which plugged the bronchial tree during intranatal respiratory efforts induced by the anoxia. Similar conditions in the human being at birth have been adequately described by Farber and Wilson.²⁰ In view of such evidence as the latter investigators present, it is impossible to avoid the conclusion that aspiration of the contents of the amniotic sac is a pathologic phenomenon ranking among the gravest consequences of anoxia.

Neurologic Symptoms After Resuscitation.—All experimental animals including those in which a state of anoxic apnea had not been reached exhibited symptoms of neural damage for shorter or longer periods after birth. In a very general way the more severe the anoxia, the more marked were the signs of brain injury. However, numerous exceptions to this rule were encountered. In some specimens whose umbilical cords were clamped for only five to seven minutes, the symptoms were as grave as in others subject to fifteen to twenty minutes of anoxia. Conversely a few of the severely anoxic guinea pigs recovered completely within a brief period of time. Thus the relation between duration of anoxia and degree of damage to the nervous system was less close than one might expect. Not only the degree of injury but also its site varied from experiment to experiment. The effect of anoxia appeared to be fortuitous and unpredictable.

All the specimens which had been rendered anoxic showed motor weakness and tremors. They were unable to get onto their feet during the first hour or more after respiration had been established. Usually they held the head to one side as though suffering from unilateral vestibular injury. They rarely cried. The animals appeared to be unaware of their surroundings and did not respond to bright flashes of light or loud sounds. These symptoms often subsided within an hour and some of the animals soon appeared to be normal in all respects. In contrast, the 90 controls righted themselves in a few minutes, cried and were very alert, although many were slightly tremulous and weak from a few minutes to an hour.

Pronounced and persistent symptoms resulted in 40 of the experimental animals. Loss of motor control of limbs and other parts of the body was a frequent sequel of anoxia. In some this flaccid paralysis lasted but a few hours; others retained it for days or until death. Loss of control of the hind limbs was commonly observed but the forelimbs were never greatly affected. Usually the hind limb paralysis was partial but in one instance a picture of complete spinal transection was

prognosis was grave. Usually the heart rate doubled or tripled within two minutes and in five minutes it had usually attained a rate approximately equal to the average rate observed before anoxia was begun. This rate, averaging 167 beats per minute, was maintained with minor fluctuations for fifteen to forty-five minutes, when an acceleration to 193 per minute occurred. This acceleration coincided with certain other changes, namely, appearance of visceral movements, passage of urine, muscular twitches, and a change in the shape of the chest during expiration which was related to the appearance of muscle tones. Another acceleration of the heart occurred at or just before the animals began to breathe. At this time the average rate increased further to 228 per minute, about that of nonasphyxiated newborn guinea pigs. The appearance and improvement of muscle tonus probably had much to do with re-establishment of normal distribution and flow of blood. We believe that the accelerations in heart rate occurred as a result of improvement of the venopressor mechanism.¹⁷

Respiratory Recovery After Anoxia.—Respiratory responses began fifteen to eighty minutes after resuscitation was started and their nature varied with the gas used. With oxygen alone, respirations usually did not begin spontaneously but started after the nervous system had recovered sufficiently to allow afferent impulses to affect the respiratory center.¹⁸ Inflation of the lungs and compression of the chest at that time led to respiratory reflexes. The inflation response could be induced as readily with pure nitrogen as with oxygen. The animals appeared to be apneic and artificial respiration had to be continued with oxygen until a high degree of somatic activity had appeared, i.e., until the respiratory center began to discharge spontaneously, before they would breathe unaided. When oxygen containing 10 per cent carbon dioxide was substituted for oxygen alone during this period, spontaneous respirations ensued immediately.

When 10 per cent carbon dioxide was employed throughout artificial respiration, spontaneous respiration was established sooner than when oxygen was used alone. Many of the animals began to breathe before afferent stimuli elicited any responses, either respiratory or of other nature. Apnea could not have existed in these specimens. No deleterious effects of the carbon dioxide were observed. In fact a greater number of animals recovered after resuscitation with the oxygen and carbon dioxide than after oxygen alone had been used. The fear of giving low concentrations of carbon dioxide to infants requiring resuscitation lest insult be added to injury already caused by metabolic carbon dioxide excess appears to be ungrounded. The actual blood content of carbon dioxide is low in neonatal asphyxia, too low perhaps for the respiratory center to respond to it, but it does respond when the level of the gas is raised. The responsiveness of the respiratory center to carbon dioxide is decreased or abolished when certain types of narcosis have been employed.¹⁹

have suffered some visual defects for they seemed to be unaware of their surroundings and would walk into objects as though blind. Vestibular disturbances have been mentioned; they persisted for only short periods of time as a rule but several animals were affected for as long as a week.

Somnolence was observed in some of the experiments. The animals closed their eyes (a phenomenon rarely observed in normal animals) and lay quietly in the cage for many minutes at a time during the first day or more. They would go to sleep while standing, the head would drop and they would topple over before awakening. Reduced activity levels were encountered several weeks after birth.

Alterations in Behavior by Anoxia.—The behavior of the young control animals was much like that of normal adult guinea pigs. They were never a feeding problem for they sought out the nipple readily and nibbled on solid food in a few days. They were alert and acutely sensitive to sound and movement in the environment. When disturbed they became startled and scurried about. The control animals avoided capture with dexterity and struggled actively when finally picked up. Even when they had become accustomed to handling they were tense and held themselves in readiness to escape the instant they were released. When introduced for the first time into a simple animal maze or when given a difficult problem to solve after they had become accustomed to the maze, they became frustrated. After initial periods of frantic scurrying they began to vocalize shrilly and sat shuddering in corners; no amount of gentle prodding or pushing could start them on their way. Urination and defecation were common reactions under such situations.

The litter mates which had been subjected to marked anoxia on the other hand were little disturbed by changes in environment. They sat apart from the rest of the litter and did not scurry for shelter when the experimenter reached into the cage. They were quite docile and relaxed when picked up and did not struggle or seek to escape when released. They seemed impervious to loud sounds and intense light. Some animals were less aware of their surroundings than others, bumping their heads against the cage walls or other obstacles. Many of these animals needed to be bottle fed, and in contrast to the controls, drank cow's milk avidly. The experimental animals were much less disturbed by the maze or problem box situation than the controls although they made more errors in reaching a solution. Position habits and stereotyped responses were common in learning situations.

Effect of Anoxia on Subsequent Learning.—Only a few attempts have been made to investigate learning ability in the guinea pig, and the methods of approach vary widely.²¹⁻²⁶ If one compares the findings of Riess²⁶ and Fjeld²⁷ who subjected different species to the same learning situation, the guinea pig rates low in its limitation of learning ability as compared to the rat, cat, and monkey. While it makes con-

seen. This involved loss of sensation as well as motor control of both hind limbs and the bladder emptied only on manual compression.

Decerebrate states were observed in many of the animals after respiration had been established. Spasticity was more prevalent and more marked in the fore- than in the hind limbs; it was sometimes accompanied by opisthotonos. In several instances the limbs became extremely stiff and could easily bear the animal's body weight without flexing. Recovery was more rapid as a rule than in cases of flaccid paralysis.

Control of other muscle groups was sometimes impaired. Paralysis of extraocular muscles, facial motor weakness, and some loss of control over the tongue and pharyngeal muscles, as shown by regurgitation of milk through the nose, occurred. Many of the animals failed to vocalize although a few cried all the time.

Persistent tremors and convulsive twitching were common symptoms of anoxic damage. In some animals, the facial as well as the limb muscles were involved. Rhythmical running movements occurred in the early phase of recovering from anoxia in many instances. In a few, locomotion subsequently became convulsive, the guinea pigs lunging forward with each attempt to run. Incoordination of the muscular effort was observed in nearly all animals. Ataxia frequently persisted for several days. Epileptiform convulsions were encountered in two animals but may have been more prevalent than this, for the specimens were not kept under constant observation.

Recovery from impairment of motor functions was highly variable. Usually it seemed to be complete in a few days or a week. Some animals remained partially paralyzed until death. Incoordination, difficulty in righting, difficulty in maintaining balance and spasticity of the limbs persisted in a few individuals.

Sensory functions appeared to be affected in varying degree after anoxia at birth. During the early hours after resuscitation hyperesthesia was observed. Many animals responded sharply even to light tactile stimuli. When they were quiet, touching the nose, limbs or body often led to convulsions or fits of running movements. The extreme irritability usually subsided in an hour or two. By the second day many guinea pigs exhibited impairment of sensation. They were less responsive to tactile and painful stimuli than their litter mates. Some appeared to have lost cutaneous sensations to a marked degree. Appreciation of pain seemed to be permanently dulled.

Hearing and vision may have been affected, although it was usually impossible to be certain of this. Most of the asphyxiated animals lost the startle response to sharp sounds. This loss was quite persistent. After an animal had recovered its other faculties so completely that by inspection it could not be distinguished from the control, it was sometimes possible to observe a marked difference between the two specimens in their response to sharp sounds. A few guinea pigs may

the blind alley happened to be. The operator observed the animal's behavior from a distance by means of a large mirror hung from the ceiling. All exits and grids were operated by remote control so that the animals were never distracted by the experimenter's presence except when they were put into the starting pen or taken from the exit. Floor plans of the maze were mimeographed, twenty on a sheet, and the exact progress of each trial as seen in the mirror was charted. Time of a given run from start to finish was measured by a stop watch. All parts of the maze received equal illumination. The exit cages were darkened by painting the insides black and roofing them over with hinged covers.

Motivation depended chiefly upon the animal's dislike for the brightly-lighted and strange confines of the problem box and upon his sense of security when burrowing in the alfalfa of the darkened exit pen. The electric stimuli encouraged his tendency to escape from the problem box. If food was an attraction, the alfalfa probably served as an additional motivating factor.

Thirty litters of animals were run at two to four weeks after delivery. A few litters were run at eight weeks. Because many of these animals were used in standardizing the test procedure, the results of only 18 litters will be considered in this report. In only a few of these litters did the test procedure vary slightly from standard conditions. As a consequence, scores on each of the four tests given were expressed as percentages of the number of trials run. The four tests were given over three consecutive days, 40 trials a day being the maximum number given on any one day. Test 1 consisted of at least 50 trials in which the blind alley and exit were changed every tenth trial. A few animals ran 60 trials. Test 2 followed Test 1 and consisted of at least 30 trials in which the pathway was alternated every fifth trial. A few animals ran 40 trials. In Test 3, of 20 trials' duration, the situation was reversed every other trial. In Test 4 the pathway was alternated in a chance sequence for 20 trials. This order of progression was used because it was found that normal animals were unable to relate the position of the blind to the correct exit if the pathway was alternated (Test 3 situation) right from the start of the experiment; even after 200 to 250 trials they failed. Such a finding is not surprising when one considers that it took Carr's rats on the average 450 trials to attain a level of 85 per cent proficiency in a simple alternation problem.²³ The limits of learning ability are higher in the rat than in the guinea pig.

In each test we compared the control against its asphyxiated litter mate in respect to running time, percentage of correct responses (obviously there are two correct responses to be made in each trial, one at the blind and one at the exits), percentage of trials run entirely correct, percentage of correct trials which were run hesitantly, and percentage duplication of errors.

In 10 of the 18 litters, the controls were definitely superior to their asphyxiated litter mates in that they made fewer errors, ran more trials entirely correctly, and were less prone to duplicate errors. Only in Test 1 was the running time significantly in favor of the controls.

siderable progress in simple mazes,²¹ the guinea pig does not solve mazes of a degree of difficulty that can be mastered by the rat. It is apparently much more plastic and variable than the rat in its attack upon simple latches and other devices, the manipulation of which will lead to food sources or escape.²⁴⁻²⁶ But it is much more irritable and distracted from its occupation than are the rat or cat by extraneous noises.²⁶

In order to compare the learning ability of the control pigs with that of their asphyxiated litter mates, we constructed a simple maze in which the pathway could be alternated to make the learning situation progressively more difficult. The animals entered the problem box (Fig. 1) from a starting pen, the door of which could be opened by remote control by the operator. A grid in the floor of this pen was used to give the animals a faradic stimulus during the initial trials if

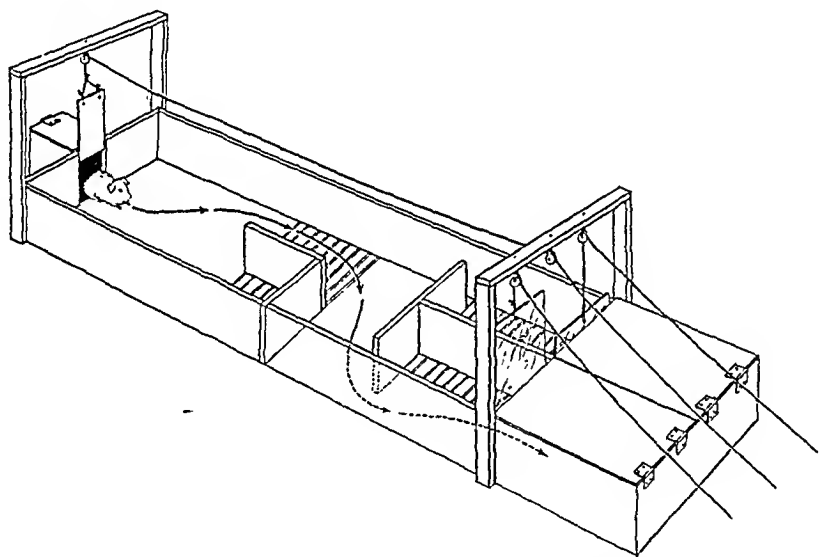


Fig. 1.—A diagram illustrating the maze used for learning tests. The arrows indicate the correct pathway run by the animal from the starting box, passing the blind alley to the darkened exit box.

they persisted in remaining there. Twenty inches from the pen door two alleys led to the two exits. One alley was a blind, and across the floor of each was another grid. The animal was again stimulated if it entered the blind alley. The entrance to each exit was narrowed by a T-shaped partition (Fig. 1). Each exit had a sliding glass panel for a door which led to a dark cage containing a nest of dry alfalfa. Only the exit behind the blind alley was open at any time. A grid had to be crossed again at each exit and an animal selecting the wrong exit was promptly stimulated. The blind alley could be shifted readily to block the opposite runway; the glass panel behind it was then raised to make the proper exit and the other panel was closed. The object was to have the animals make the association that the correct exit was always behind the blind alley no matter on which side

that these tests were run two, four, and in some instances, eight weeks after operation. At these times, it was impossible by mere observation alone to detect overt differences in behavior between these asphyxiated animals and their litter mates, or between them and any other normal guinea pig in the animal colony.

TABLE I. PATHOLOGIC REPORT

EXPER. NO.	ANIMAL NO.	ANOXIA		DAY OF DEATH	EVIDENCE OF DAMAGE
		MIN.	SEC.		
47:40	3	5	30	46	Slight cell loss in pyramidal and ganglionic layers of cortex? Possible loss of Purkinje cells of cerebellum
15:41	1	0	0	43	Normal control brain
	2	6	0	43	No pathology?
9:41	1	0	0	84	Normal control brain
	2	7	10	84	Pathology questionable; slight atrophy?
46:39	1	0	0	36	Normal control brain
	2	7	30	36	Slight cell loss in pyramidal and ganglionic layers of cortex?
	3	7	55	36	Slight atrophy of frontal lobe with cell loss in ventral part
6:41	1	0	0	34	Normal control brain
	3	7	45	34	Slight cell loss in pyramidal and ganglionic layers of cortex?
83:41	3	11	30	2	Marked early disseminated necrosis of brain and cord; chromatolysis; edema; small hemorrhages, especially in hippocampus; ventricular enlargement
4:41	1	0	0	14	Normal control brain
	2	12	45	14	Atrophy with slight ventricular enlargement, especially in rostral hypothalamus, thalamus and midbrain; devastation areas
18:42	1	0	0	½	Normal control brain
	2	14	0	½	Petechial hemorrhages scattered throughout brain
1741:B	1	0	0	43	Normal control brain
	2	14	0	43	Marked generalized atrophy with hyperchromatic, pyknotic cells; pial thickening
	3	16	30	2	Disseminated necrosis; chromatolysis beginning
53:40	1	0	0	32	Normal control brain
	2	15	54	32	Generalized atrophy with ventricular enlargement; slight cell loss
52:41	2	16	30	1	Beginning disseminated foci of necrosis; ventricular enlargement; slight edema
37:42	3	17	0	23	Glial scars; slight cell loss in pyramidal and ganglionic layers of cortex?
45:42	1	0	0	5	Normal control brain
	2	17	19	5	Glial proliferation; pyramidal cell damage; ventricular enlargement
56:42	1	0	0	9	Normal control brain
	2	17	30	9	Cortical atrophy with marked loss of pyramidal cells; gliosis generalized, and specific foci in substantia nigra; slight ventricular enlargement
76:41	1	0	0	3	Normal control brain
	2	21	0	3	Early disseminated necrosis; ventricular enlargement; hemorrhages in cerebral cortex, mesencephalon, medulla oblongata

In two other litters the difference in performance was only slightly in favor of the controls and in six litters the differences were reversed in favor of the asphyxiated animals. It is probably significant that in these last six litters the duration of asphyxiation had been short (three to five minutes) in five cases. The asphyxiated animal in the sixth pair had no litter mate but was run against a control animal of the same age which likewise had no litter mate. The performance of this particular control for some unknown reason was the poorest of all animals tested, controls and asphyxiated animals included.

There was little difference in the hesitancy scores in the majority of instances. This may be explained by comparing the behavior of the two groups in the learning situation. The controls were more alert and irritable and tended to "freeze" at the slightest extraneous noise particularly during the first 30 or 40 trials. They were more aware of the strangeness of the problem situation than their more asphyxiated litter mates. The asphyxiated pigs tended to repeat errors more than the controls. That is, in a given trial they continued to re-enter the blind alley or wrong exit several times in spite of the faradic stimuli they received. They seemed on the whole less disturbed by such punishment than their controls.

Repetition of errors in this way led to the development of a stereotyped pattern of behavior. When correct runs were eventually made, the animal hesitated in front of the blind and the wrong exit each time before selecting the alternate correct pathway. Because of these two different factors, distractibility and stereotyped response, the hesitancy scores in general tended to equate as did the time score.

The controls on the other hand were much more plastic and variable in their selection of a pathway and in the manner in which they traversed the maze in consecutive trials. When blocked they readily tried other routes. Such adaptability and variability in response was observed in the normal guinea pig under other experimental learning situations.²⁴⁻²⁶ In this respect they were more pliable than normal rats. It is interesting to note Mair's^{29, 30} finding of an increase in stereotyped behavior in rats after cortical lesions experimentally induced by thermocautery. Chang and Liu³¹ have reported that ligation of the two common carotids in rats led to an increase in errors and running time over their own previous scores in the maze situation. The shock of operation was ruled out, in that another series of animals operated but without ligation of the vessels showed no change in performance. These authors apparently failed to appreciate the fact that they were dealing with effects of anoxia. However I. C. Wen³¹ who carried out the histologic study of these brains, found no evidence of degeneration of nervous tissue.

In general, then, we can say that the asphyxiated animal tends to make more errors, tends to duplicate the same error in a given trial, and becomes much more stereotyped in his responses, even when they are correct, than does his litter mate control. It should be recalled

minutes after the cessation of intrauterine respiratory efforts, and resuscitation in this group was delayed until the fetal heartbeat was weak and often too feeble to palpate. Anoxia thus induced led to the characteristic picture of asphyxia pallida; namely, apnea, bradycardia, atonia, cold pale skin, and dilation of the visceral capillary beds.

The only effective method of resuscitating such apneic fetuses was to inflate the lungs rhythmically and gently with oxygen or with oxygen containing 10 per cent carbon dioxide. Respiration was established sooner with the gas mixture than with oxygen alone. All efforts to revive fetuses by mechanical or electrical stimulation or by the injection of respiratory stimulants proved ineffectual.

The behavior of resuscitated animals was compared with that of their litter mate controls until overt differences were no longer noticeable. The animals were then subjected to a modified maze situation in order to discover possible impairment of learning ability resulting from anoxial damage to the central nervous system. When all observations and tests were completed, the brains of the experimental animals and their controls were removed and prepared for histologic study.

The following statements summarize the results of experimentally induced asphyxia neonatorum in guinea pigs:

1. Respiratory movements in utero continued longer after clamping the uterine arteries than the umbilical cord. This finding is related to the total volume of oxygenated blood available to the fetus; there is a placental reserve when the uterine vessels are clamped.

2. Within two minutes after clamping the uterine or umbilical vessels the heart slowed to half its normal rate. The heart could be palpated for twelve to fifteen minutes after clamping but grew progressively weaker and slower with prolonged anoxia. When oxygen or oxygen-carbon dioxide were administered, there was an immediate return in strength and rate of the heart. Acceleration from this point on was not gradual but saltatory, further increments coinciding with the appearance of visceral movements, urine passage, muscular twitching, improvement of thoracic tonus and finally a last increase as breathing began.

3. It required fifteen to eighty minutes to resuscitate apneic fetuses but the nature of initial respiratory responses varied with the gas used. Respirations did not begin spontaneously with oxygen alone until after the nervous system had recovered sufficiently to allow afferent vagal and spinal impulses to affect the respiratory center reflexly. Ten per cent carbon in oxygen brought about a spontaneous response of the respiratory center sooner than oxygen alone, and before the center could be made to respond reflexly.

4. Asphyxiated guinea pigs lost more weight in the first three days of life than did their litter mate controls. Their weight average over the first four weeks also was lower than the average of controls.

5. All asphyxiated animals exhibited symptoms of neural damage for shorter or longer periods after birth. The following phenomena were noted: (1) weakness and tremors; (2) delayed and incoordinated efforts to right; (3) flaccid paralysis, particularly of the hind limbs and often lasting for several days; (4) spastic paralysis, particularly

Pathology Induced by Anoxia.—Gross pathology in the specimens which could not be resuscitated and those which lived but a short time has been mentioned. Aspiration of meconium in the amniotic fluid led to failure of the alveoli to expand with air. Overexpansion of the lungs with oxygen in resuscitation occasionally produced pneumothorax. Hemorrhages were sometimes encountered and were more commonly found in the lungs, liver, and other visceral organs than elsewhere. This was probably related to the gravitation of blood into the deeper organs in asphyxia pallida. In only one instance did we observe gross hemorrhage in the cranium.

We were especially concerned with the changes inflicted upon the nervous system by anoxia. All the brains of control and experimental animals were preserved and are being sectioned serially. At present a preliminary report can be presented, but complete studies have been made on only 17 specimens together with normal litter mates as controls. These are listed in Table I.

It will be observed that the histopathology was slight or questionable in the six experimental animals which had suffered less than eight minutes of anoxia. Definite pathologic findings were present in all the rest. However, there is not a constant relationship between degrees of anoxia and brain damage. The animal asphyxiated for eleven and one-half minutes showed more profound brain lesions than any of the others. One asphyxiated for seventeen minutes was less damaged than several with shorter periods of anoxia. One cannot safely predict that a brief period of anoxia will fail to affect the infant nor that prolonged anoxia surely will lead to total destruction.

The obvious conclusion to be reached from these preliminary histologic studies is that anoxia produced definitely demonstrable brain lesions in 65 per cent of the animals in question. The brains of control litter mates showed no pathology at all. More detailed consideration will be given to this aspect of the present study at a later time when all specimens have been prepared and examined. Five of the seventeen asphyxiated animals whose brains were studied had been subjected to the learning tests and four of them were poorer than their normal controls. All five showed pathologic changes in the central nervous system, although this was slight in one specimen.

Summary

By clamping either the uterine vessels or the umbilical cords, it was possible to induce intrauterine anoxia experimentally in guinea pig fetuses at or near term. Prior to this procedure the mother's abdomen had been anesthetized locally and one fetus delivered to serve as a control animal. Fifty-eight asphyxiated fetuses were delivered as soon as intrauterine respiratory movements, induced by the anoxia, became weak or had just ceased. Forty-five other fetuses were delivered some

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PLACENTAL TRANSMISSION OF SULFATHIAZOLE AND SULFADIAZINE AND ITS SIGNIFICANCE FOR FETAL CHEMOTHERAPY

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IN THE management of infectious diseases complicating pregnancy it is rarely necessary to give separate consideration to the welfare of the fetus. The interests of the latter are usually best served by those methods of treatment which are aimed directly at the control or eradication of the maternal disease. A notable exception to this generalization is found in the treatment of syphilis in pregnancy, for here consideration of maternal factors, except in special circumstances, is distinctly secondary to and occasionally at variance with the major objective, fetal prophylaxis. Most commonly little if any change in the status of the maternal syphilitic infection occurs during pregnancy, whereas the issue to the fetus is paramount. A somewhat comparable condition exists in the case of gonococcal infection of the lower genital tract. Here too the mother may herself undergo no significant change as a result of pregnancy and labor, but all too frequently she inoculates the eyes of her offspring with an organism which is still one of the commonest causes of blindness in children in this country (Berens, Kerby, and McKay, 1935).

In instances such as these it behooves the obstetrician to accord special consideration to the specific prophylactic requirements of the fetus. Despite the gratifying reduction in the incidence of gonococcal ophthalmia which has followed upon the routine instillation of silver nitrate into the eyes of the newborn, every large obstetric clinic is still confronted with an occasional case of this disease. Likewise in instances of severe intrapartum infection, although the mother may undergo rapid improvement following delivery, the fetus is poorly equipped to combat the infection acquired in utero and often succumbs to it during the

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of forelimbs and accompanied by opisthotonos; (5) convulsive twitching and rhythmical running movements; (6) epileptiform convulsions; (7) paralysis of extraocular muscles, facial motor weakness, and some loss of control over tongue and pharyngeal muscles; (8) early hyperesthesia followed by hyposensitivity; (9) somnolence and reduced activity levels; (10) perhaps some impairment of hearing and vision. The degree of injury and its site varied from animal to animal in a fortuitous manner; there was no precise correlation between the duration of anoxia and the severity of damage.

6. Asphyxiated guinea pigs exhibited noticeable behavioral differences when compared with control animals during the first two weeks. In general they were not greatly disturbed by changes in their environment. They became quite docile and were flaccid when handled. Loud sounds did not elicit the normal startle response. They did not respond briskly to faradic stimulation. Many of them presented feeding problems and were weaned on cow's milk, a food which the controls refused to take. They were not as active as normal guinea pigs and were not as tense and irritable in learning situations.

7. When confronted with a simple maze and alternation problem, the asphyxiated animals made more errors and duplicated the same errors more frequently than did their litter mate controls. Even in correct trials their behavior was remarkably stereotyped and showed little of the plasticity and variation encountered in the responses of the control animal.

8. The central nervous system of 65 per cent of the experimental animals studied to date showed histopathologic changes. All control brains were normal and only questionable or slight pathologic findings could be seen in the remaining asphyxiated animals. Changes in the first few days after anoxia had been induced included early disseminated necrosis, edema, chromatolysis, scattered petechial hemorrhages and enlargement of the ventricles. Glial proliferation appeared by five days and was marked at nine days. In older specimens loss of nerve cells led to local or generalized atrophy of the brain. Destruction of pyramidal cells in the cerebral cortex was observed. Necrosis and atrophy were not always related to hemorrhages.

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them in respect to therapeutic efficacy, pharmacology, and toxicity, so that predictions cannot safely be made concerning one compound on the basis of knowledge of the others. Sulfanilamide, sulfapyridine, and sulfadiazine, for example, diffuse freely into the cerebrospinal fluid, their concentration there approximating that in the blood; yet the passage of sulfathiazole into the cerebrospinal fluid is very poor. Although sulfanilamide is found in greater concentration in the red cells than in the blood plasma, the reverse is true of sulfapyridine, sulfathiazole, and sulfadiazine (Cooper, Gross, and Hagan, 1942; Ratish, Shackman, and Bullock, 1942). Data concerning placental transmission are limited at present to sulfanilamide. The present investigation was therefore undertaken to ascertain the permeability of the placenta to the currently popular sulfonamide derivatives, sulfathiazole and sulfadiazine.

TABLE I. PLACENTAL TRANSMISSION OF SULFATHIAZOLE FOLLOWING INGESTION OF SINGLE 5 GM. DOSE DURING LABOR

PATIENT	TIME HOURS:MINUTES	SULFATHIAZOLE MG. PER CENT			
		MATERNAL BLOOD		FETAL BLOOD	
		FREE	TOTAL	FREE	TOTAL
I. G.	1:00	0	0	0	0
B. J.	1:20	0	0	0	0
S. R.	1:40	0	0	0	0
P. W.	3:40	Trace	Trace	Trace	Trace
A. J.	4:30	Trace	Trace	Trace	Trace
C. S.	5:45	1.1		0.6	0.9
D. E.	6:00	2.1		Trace	
M. R.	11:00	Trace		Trace	

Observations

A single oral dose of 5 Gm. of sulfathiazole was given during labor to a group of eight women. When delivery occurred, between one and eleven hours later, samples of maternal venous blood and fetal blood from the umbilical vein were obtained, and sulfathiazole determinations performed (Bratton and Marshall, 1939). Results are shown in Table I. In an additional case, 8 Gm. of the drug were administered in divided doses over a period of six hours. Determinations on blood obtained at the time of delivery revealed 3.4 mg. per cent and 2.5 mg. per cent of free sulfathiazole in the maternal and fetal blood, respectively, with a trace of the conjugated form in each. In a tenth case, 5 Gm. of the drug were given in repeated doses beginning four and one-half hours before delivery. Sulfathiazole concentrations in the maternal plasma and cord blood serum were 3.4 mg. per cent and 1.2 mg. per cent, respectively.

As has already been pointed out in a study based in part on these findings (Speert, 1942), absorption of orally administered sulfonamides is very poor during labor. The data in Table I show that in only two cases were measurable quantities of sulfathiazole detected in the maternal blood. In the two additional cases mentioned, small amounts of the drug were also demonstrated. Although indicating the passage of sulfathiazole across the placenta, these results were too meager and the maternal blood levels too low to permit a statement of the quantitative aspects of placental transmission.

early neonatal period. Thus in cases of intrapartum infection, the outlook is much more serious for the infant than for the mother. Slemons (1918) has reported a fetal and neonatal mortality of 40 per cent, the figures of other authors ranging between 18 and 61 per cent.

The organisms which are most frequently encountered in severe neonatal infections, such as the hemolytic streptococcus, staphylococcus, and colon bacillus, are among the most responsive to sulfonamide treatment. The sulfonamide drugs, similarly, are highly effective against the gonococcus and have been widely employed in the treatment of gonococcal ophthalmia (Wong, 1942). Therefore, if one is to re-examine these problems with the view of extending the scope of fetal prophylaxis and intrauterine therapy, it becomes profitable, indeed necessary, to inquire into some aspects of the pharmacology of the currently available sulfonamide drugs. Foremost among these problems is the question of placental transmission. Do the sulfonamide derivatives reach the fetus after their administration to the mother? If so, how soon and in what relative concentration? How is the fetus most effectively treated in utero?

Sulfanilamide passes rapidly across the placenta into the blood stream of the fetus and into the amniotic fluid, following the ingestion of the drug by the mother. This fact was first demonstrated in rabbits by Lee, Anderson, and Chen in 1938. In independent experiments performed at about the same time, the rabbit placenta was found to be equally permeable to the drug at various stages of pregnancy (Speert, unpublished). Similar findings have been demonstrated in the rat (Speert, 1940). As has been reported by Barker (1938), Speert (1938), and Dignonnet (1939), the human placenta is likewise freely permeable to sulfanilamide, equilibrium between mother and fetus being attained within three to five hours after the institution of oral therapy. These data extended to the fetus the previously demonstrated fact that sulfanilamide distributes itself rather uniformly throughout the body and appears in approximately equal concentrations in the various tissues and body fluids (Marshall, Emerson, and Cutting, 1937).

So rapid have been the advances in bacterial chemotherapy during the past few years that pharmacologic data have hardly kept abreast with the zealous clinical use of the newer sulfonamide derivatives. Indeed, no sooner has the pharmacology of a new member of this group become well studied than this drug has found itself forced into the background by a newer and better preparation. Such has been the story of sulfanilamide, sulfapyridine, and sulfathiazole. It seems somewhat paradoxical that the most completely studied member of the sulfonamide group, namely sulfanilamide, is much less commonly used at present than its more popular but less well studied successors, sulfathiazole and sulfadiazine.

Despite many basic points of similarity among all members of the sulfonamide family, sufficiently numerous are essential differences among

TABLE III. PLACENTAL TRANSMISSION OF SULFADIAZINE FOLLOWING INGESTION OF SINGLE 5 GM. DOSE DURING LABOR

PATIENT	WEIGHT KG.	TIME HOURS:MIN- UTES	SULFADIAZINE (FREE) MG. PER CENT		
			MATERNAL BLOOD	FETAL BLOOD	AMNIOTIC FLUID
E. M.	75	2:00	1.3	0.8	
K. K.	76	2:20	2.8	2.3	0.7
W. O.	61	2:30	1.1	0.5	0.1
S. H.	73	4:30	0.9	0.8	1.0
L. G.	71	4:50	0.7	0.5	

To another series of 11 patients 5 Gm. of the soluble sodium sulfadiazine were therefore administered intravenously at intervals varying between thirty minutes and eight and one-half hours before delivery. This resulted in an immediate maternal blood concentration exceeding 20 mg. per cent, with a fetal blood level of about 10 mg. per cent within thirty minutes (Table IV). The drug disappeared very slowly from the maternal blood during the next eight hours, yet the sulfadiazine remained at a fairly constant level in the fetal blood during this period. Equilibrium between the two blood streams with respect to sulfadiazine was attained within two and three-fourths hours.

It is interesting to note that the concentrations of sulfadiazine in the cord blood were consistently higher than those of sulfathiazole following the administration of equal doses of the two sodium salts. As was found with sulfathiazole, sulfadiazine also passed into the amniotic fluid but was usually found there in smaller concentrations than in the fetal blood. The failure of the sulfadiazine concentration in the amniotic fluid to exceed that in the fetal blood may be due to the slower excretion of this drug by the fetal kidneys.

TABLE IV. PLACENTAL TRANSMISSION OF SULFADIAZINE FOLLOWING INTRAVENOUS INJECTION OF 5 GM. OF THE SODIUM SALT DURING LABOR

PATIENT	WEIGHT KG.	TIME HOURS:MIN- UTES	SULFADIAZINE (FREE) MG. PER CENT		
			MATERNAL BLOOD	FETAL BLOOD	AMNIOTIC FLUID
G. M.	54	0:30	20.8	9.7	1.2
L. H.	56	0:30	20.1	11.5	0.6
A. B.	76	1:00	13.9	8.9	0.6
D. H.	64	1:00	13.5	11.8	1.5
V. P.	59	1:00	14.8	9.4	4.4
M. A.	60	2:45	11.7	11.6	5.7
B. G.	67	4:00	9.8	10.6	3.4
J. T.	60	4:45	12.5	11.1	
E. B.	88	6:40	10.9	11.0	6.9
V. D.	87	7:00	6.5	8.0	8.5
K. S.	64	8:30	9.1	8.4	7.2

Comment

The present study has demonstrated the human placenta at term to be freely permeable to sulfathiazole and sulfadiazine, as has been established previously for sulfanilamide.

Following the intravenous injection of a single dose of sodium sulfathiazole or sodium sulfadiazine during labor, equilibrium between maternal and fetal blood with respect to these compounds was established

Sodium sulfathiazole, because of its ready solubility, can be administered intravenously. Immediately following the injection of 5 Gm. of this compound (100 c.c. of a 5 per cent solution in sterile distilled water), a blood concentration of approximately 20 mg. per cent is established. Since this mode of administration seemed well adapted to the study of placental transmission, a group of seven additional patients were so treated during labor, at intervals ranging between fifteen minutes and sixteen hours before delivery. In addition to maternal and cord blood, amniotic fluid was also analyzed for its sulfathiazole content. Ample amounts of amniotic fluid could usually be collected in the gush which follows immediately upon the heels of the infant. Contamination with blood was minimal, but moderate amounts of vernix and meconium were often present. These were removed by filtration and centrifuging. The turbid supernatant fluid was then precipitated and incubated at 37° C. for thirty minutes, during which time it became sufficiently clear to permit analysis after filtration. In instances where the fetal head was engaged and a bag of forewaters was present, the sulfathiazole concentration of the amniotic fluid in the latter was appreciably lower than that contained in the fundus. The data therefore represent analyses of only the fluid which followed delivery of the infant. Results are shown in Table II.

TABLE II. PLACENTAL TRANSMISSION OF SULFATHIAZOLE FOLLOWING INTRAVENOUS INJECTION OF 5 GM. OF THE SODIUM SALT DURING LABOR

PATIENT	WEIGHT KG.	TIME HOURS:MIN- UTES	SULFATHIAZOLE (FREE) MG. PER CENT		
			MATERNAL BLOOD	FETAL BLOOD	AMNIOTIC FLUID
E. P.	60	0:15	20.7	5.6	
R. J.	61	1:00	11.1	5.6	2.6
A. B.	54	2:40	6.8	7.0	1.8
E. W.	77	3:30	10.0	7.6	3.8
A. R.	80	6:15	5.2	5.1	7.1
J. W.	61	13:00	2.4	3.0	3.6
E. B.	68	16:00	1.3	1.8	2.6

Sulfathiazole appeared in the fetal blood almost immediately after administration of the sodium salt to the mother. Within fifteen minutes, a concentration of 5.6 mg. per cent was present. Despite the decline in the maternal blood level during the next six hours, little variation was observed in the cord blood concentrations. Equilibrium between the two blood streams with regard to sulfathiazole appeared to be attained within about two and one-half hours. The drug was also present in the amniotic fluid, appearing there in smaller amounts than in the fetal or maternal blood until about six hours after administration. Thereafter the sulfathiazole concentration in the amniotic fluid consistently exceeded that present in either the fetus or mother. This was probably due to excretion of the drug into the amniotic fluid by the fetal kidneys.

In an attempt to obtain parallel data concerning the transfer of sulfadiazine from mother to fetus, a series of 5 patients were given a single oral dose of 5 Gm. of the drug during labor. Delivery occurred in each instance between two hours and four hours and fifty minutes later. Analyses of cord blood and amniotic fluid revealed the passage of the drug to the fetus (Table III). Here also, however, as in the case of the patients receiving sulfathiazole by mouth during labor, absorption was poor and the maternal blood levels very low, resulting in correspondingly low sulfadiazine concentrations in the fetal circulation.

to delivery would seem indicated as a prophylactic measure against the development of gonococcal ophthalmia in the newborn. Such a procedure might be compared to the addition of a bactericidal concentration of a sulfonamide to a culture medium prior to its inoculation with the gonococcus. In addition to the lesser degree of toxicity of sulfadiazine, this drug has the further advantage over sulfathiazole of producing a higher and better sustained blood level in the fetus after administration of the sodium salt to the mother. We have found maternal blood concentrations of approximately 10 mg. per cent as long as twelve hours after the intravenous administration of a single 5 Gm. dose of sodium sulfadiazine to pregnant women of average weight.

The infants in this study all appeared perfectly normal at birth. There was no suggestion during their neonatal course that the single dose of sulfonamide received in utero had in any way affected their development. Under the exaggerated conditions of animal experiments, however, sulfanilamide has been charged with causing an increased neonatal mortality in rabbits (Adair, Hesseltine, and Hae, 1938). When administered in large doses to rats throughout pregnancy, an increased intra-uterine and postnatal mortality, decreased litter size, and diminished birth weight resulted (Speert, 1940). In addition, a most striking effect of sulfanilamide therapy was the selective stunting of growth among the offspring, many runts resulting. The only patient in whom we have had the opportunity to observe the effects of prolonged sulfanilamide medication during pregnancy received this drug throughout the entire last trimester because of a chronic meningitis of undetermined etiology. The concentration of the free drug in the blood ranged between 2.4 and 4.5 mg. per cent. Spontaneous labor and delivery ensued three days beyond the expected date of confinement, with the birth of a living infant weighing only 2,110 Gm. Despite its low birth weight, this infant gave evidence of being mature by all other criteria, including the blood picture, serum proteins, and roentgenologic studies of the ossification centers. In a recent report, Heekel (1941) has also presented evidence of possible fetal injury resulting from sulfanilamide therapy, in the form of severe anemia and jaundice in the infant.* Indications rarely arise for prolonged sulfonamide treatment during pregnancy. Until the chronic administration of sulfathiazole and sulfadiazine have been proved to be equally safe for the human fetus as for the mother, it might be well, therefore, to bear in mind the possible hazards to the fetus resulting from prolonged exposure to these drugs in utero.

Conclusions

Sulfathiazole and sulfadiazine, like sulfanilamide, diffuse readily across the placenta. Following the intravenous administration of a

*Ginzler and Chesner (Am. J. Obst. & Gynec. 44: 46, 1942) have recently reported two additional possible instances of toxic manifestations in the newborn infant resulting from sulfanilamide administered to the mother.

within two to three hours. Occasional cases in which the maternal was slightly in excess of the fetal blood level after three hours may be explained on the basis of a lower hematocrit value for the maternal blood, with a resultant greater proportion of plasma to red cells.

Experiments by Flexner, Pohl, and Gellhorn on the goat, pig, cat, rabbit, rat, and guinea pig, and by Snyder and Speert on the rabbit have revealed marked differences in the rate of placental transmission of other substances at earlier stages of pregnancy. Little is known concerning the permeability of the placenta to sulfonamides at stages other than term. The scant data which we have, however, has shown no essential variations from those previously described. In a small series of pregnant rabbits which were injected subcutaneously with a solution of sulfanilamide containing 0.2 Gm. per kilogram body weight, equilibrium between maternal and fetal blood was reached within five hours at stages as early as the twenty-fourth day. The drug was also found to diffuse freely into the amniotic fluid at these early stages. Opportunity was afforded for the study of the placental transmission of sulfapyridine during mid-pregnancy by a patient undergoing treatment for pneumonia at the end of the fifth month. After receiving 7 Gm. of the drug orally over a period of ten hours she delivered a living abortus spontaneously. The concentration of free sulfapyridine in the maternal blood at delivery was 6.7 mg. per cent, in the cord blood, 5.0 mg. per cent. Among the present series of patients receiving sodium sulfadiazine was one (L. H.) in premature labor at thirty weeks. Comparison with the results obtained in the case of G. M., who delivered after the same time interval at term, reveals no significant difference in placental transmission of sulfadiazine at these stages. It is obviously impossible to make a quantitative comparison of the rate of transfer of the sulfonamides across the placenta at various stages of pregnancy on the basis of these few observations. Yet they do demonstrate the passage of these substances to the fetus in concentrations of therapeutic and perhaps potentially toxic significance at stages antedating the onset of viability.

It would seem reasonable, therefore, to administer sulfonamides during pregnancy for fetal as well as maternal indications. In cases of intercurrent or intrapartum intrauterine infections caused by organisms which are susceptible to the sulfonamides, the fetus may be effectively treated by the drugs administered to the mother. Slemons (1915, 1918) has shown in cases of prolonged labor with ruptured membranes that bacteria enter the placenta by way of the amnion and the amniotic fluid, with subsequent invasion of the fetal vessels and the production of a so-called placental bacteremia. The presence of an adequate sulfonamide concentration in the amniotic fluid would therefore serve as a protective agent for the fetus at the first line of defense. Also, in cases of gonococcal infection of the maternal lower genital tract, the establishment of an adequate sulfonamide concentration in the fetus prior

THE COLOSTRUM INTRADERMAL TEST FOR THE DIAGNOSIS OF PREGNANCY*

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IN SEPTEMBER, 1940, Drs. Falls, Freda, and Cohen presented their intradermal test for the diagnosis of pregnancy. The testing material was pooled colostrum, manually expressed from the breasts of normal primiparas, 28 or more weeks pregnant. This colostrum was diluted with an equal amount of sterile, normal saline solution to which was added $\frac{1}{10}$ e.e. of 1:100 merthiolate preservative for every 10 c.c. of colostrum mixture.

One-fiftieth of a cubic centimeter was injected intradermally on the flexor surface of the forearm and the reactions were read at ten-, thirty-, and sixty-minute intervals along with a sterile, normal saline control.

The patient tested was considered pregnant if the injected material produced no enlarging wheal or red areola, or if a red areola developed but vanished completely within sixty minutes. This latter reaction was termed a weak pregnancy reaction.

A nonpregnant reaction was one with an enlarging wheal surrounded by a red areola which persisted for more than one hour. The original investigators have called any tests with an areola at the end of sixty minutes a nonpregnant reaction.

Using this technique, these workers reported 98 per cent of accuracy in pregnant women and 96 per cent of accuracy in nonpregnant women. Since publication of the original article, a number of men have reported varying results. Some have been good, others fair or poor. To date no other group of investigators has obtained as high a degree of accuracy as the original authors. None of these investigators have attempted to clarify the mechanism of this reaction.

The purpose of this paper is to present the results of the intradermal test for the diagnosis of pregnancy done on a series of pregnant and nonpregnant women. Some interesting findings are also discussed.

Colostrum was manually expressed from the breasts of primiparous women, twenty-eight to thirty-seven weeks pregnant. There was no particular time in the third trimester, except perhaps in the latter part, that colostrum was more abundant. The amounts of colostrum that could be expressed from the breasts of primiparas varied from little to as much

*Presented at a meeting of the Chicago Gynecological Society, May 15, 1942.

single 5 Gm. dose of sodium sulfathiazole or sodium sulfadiazine to the mother during labor, these drugs appear in the fetal blood almost immediately and are retained there in therapeutically effective concentrations for at least six hours in the case of sulfathiazole and considerably longer in the case of sulfadiazine. Equilibrium between maternal and fetal blood is established within three hours. Sodium sulfadiazine results in a higher concentration of the drug in the fetal blood than does an equal dose of sulfathiazole. These drugs appear also in the amniotic fluid, but more slowly than in the fetal blood.

The intravenous maternal injection of sodium sulfathiazole or sodium sulfadiazine is suggested as a method of treating the fetus in utero in cases of intercurrent or intrapartum infection caused by susceptible organisms. When the lower genital tract of the mother harbors the gonococcus, the establishment of an adequate sulfathiazole or sulfadiazine concentration in the fetus prior to delivery would appear indicated as a prophylactic measure.

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The author discusses the excellent results obtained in 17 cesarean sections done under intravenous anesthesia. Krebs feels this method is indicated when the mother has complicating cardiac or respiratory disease. He notes that all infants cry spontaneously, but he has found a danger period for the infant during the first few minutes after severance of the cord until the respiratory mechanism is well established.

The 9 colostrum specimens used in this series were obtained from one patient with toxemia, one colored woman, one Mexican woman, a blonde, a redhead, three brunettes, and in addition one pooled colostrum sample collected and prepared by Dr. Freda. All of the above individuals had negative Kahn and Wassermann tests. The colostrum was used for four or five months, checked for total protein and nonprotein nitrogen, then discarded.

The unfiltered colostrum with merthiolate preservative, prepared by the Falls-Freda technique, was used in the known pregnant group 103 times and in the known nonpregnant group 43 times. All of the other tests were run with the colostrum filtrate samples.

In the known pregnant group of patients an unfiltered and a filtered colostrum sample differed from each other in reaction eight times (see (1) and (2) in Table II). These two samples of colostrum differed from one another in the nonpregnant cases six times. The other colostrum specimens differed from one another in reaction on several occasions. The colostrum samples were found to vary in total protein and nonprotein nitrogen content. In all but one case the unfiltered colostrum had a higher total protein and nonprotein nitrogen value than the filtered colostrum.

TABLE II. NONPROTEIN NITROGEN AND TOTAL PROTEIN

COLOSTRUM PT.	COLOR	PARITY	GESTATION	TYPE SAMPLE	TOTAL PROTEIN	NITROGEN NONPROTEIN
Mrs. M.	redhd.	G, 1; P, 0	(1) 33 wk.	Filtrate	3.86	108
Mrs. M.	redhd.	G, 1; P, 0	(2) 32 wk.	Nonfiltrate	6.83	204
Mrs. A.	br.	G, 1; P, 0	28-32 wk.	Nonfiltrate	7.14	184
Mexican	br.	G, 1; P, 0	32 wk.	Filtrate	3.32	88
Mrs. B.	col.	G, 1; P, 0	28 wk.	Filtrate	8.16	144
Toxemia	br.	G, 1; P, 0	36 wk.	Filtrate	0.36	92
Toxemia	br.	G, 1; P, 0	36 wk.	Nonfiltrate	7.97	124
Mrs. T.	br.	G, 1; P, 0	34 wk.	Nonfiltrate	9.10	164
Pooled	-	-	-	Nonfiltrate	7.20	216

In 5 instances the residue and filtrate of a colostrum sample gave identical reactions. In the pregnant group the filtrate and nonfiltrate gave about the same percentage of error, i.e., 1 incorrect out of 2. In the nonpregnant group, the percentage of error for the filtrate was 1 incorrect out of 6, and for the nonfiltrate 1 incorrect out of 8.

TABLE III. PERCENTAGE OF INCORRECT REACTIONS

	PREGNANT	NONPREGNANT
Filtrate	36 incorrect out of 95 tests. 1:2½	10 incorrect out of 62 tests. 1:6
Nonfiltrate	40 incorrect out of 86 tests. 1:2	4 incorrect out of 31 tests. 1:8

All colostrum samples that were passed through the Berkefeld filter were found to be sterile as mentioned. The unfiltered colostrum samples containing 1:1000 merthiolate were cultured on blood-agar plates within four days of the time of collection and were found to be contaminated with staphylococcus organisms. However, after standing in the refrigerator for several months, these samples were found to be sterile.

Recently one woman's arm was severely infected from the intradermal injection of a freshly prepared colostrum specimen contaminated with *Bacillus pyocyaneus*. Two other patients injected with the same specimen developed mild infections. The possibility of reactions from toxin formed in a contaminated colostrum specimen is not likely but must be

as one ounce at one manual expression.* Most of the colostrum samples were diluted with an equal amount of sterile, normal saline solution and passed through a Berkefeld filter. These specimens were uncontaminated with bacteria. The colostrum from each individual was collected and kept in a separate glass vial. Usually no preservative was used. Some of the specimens contained 1 c.c. of 1:1000 merthiolate preservative for each 9 c.c. of the colostrum mixture. This was the same proportion as the 1:100 merthiolate used in the colostrum samples prepared by the Falls-Freda technique. All the colostrum preparations were kept in a refrigerator when not in use.

The tests of this series were performed and read by one individual (L. B. D.). Dr. Freda was consulted personally about the test on several occasions.

Before this series was begun, 30 known pregnant and at least 25 known nonpregnant women were tested to perfect the technique of reading the reactions. These cases were not included in this report.

At all times individual colostrum samples were used, except in a series of 48 cases checked with "pooled" colostrum prepared by Dr. Freda. In 56 women of the known pregnant group and in 41 women of the known nonpregnant group, two different colostrum specimens were injected at the same time. In all instances the test was run with saline controls. In approximately one-third (89) of the cases a merthiolate control was used. The merthiolate control consisted of sterile, normal saline solution containing 1:1000 merthiolate preservative in the same proportion as that used in the colostrum specimens.

In each case the test was read at ten-, thirty-, and sixty-minute intervals and the results recorded on a card containing the information as shown in Table I.

TABLE I. DATA INFORMATION

Name	Address	Telephone
B. or W. (Bl. Br. Rd.)	Age	Marital-occup. status
L.N.M.P.	Due date	Weeks gestation
Skin sensitivity		
Reaction:	Date:	
10" } readings	"	
30" }	"	
60" }	"	
Type colostrum: (1)	(2)	(3)
Remarks: Reaction to saline and merthiolate controls.		
Impression: Pregnant or nonpregnant reaction.		

*It was observed during the collection of colostrum samples from various women that those with poor, fair, good, or excellent amounts of colostrum were found during the first ten days of their post-partum periods to have correspondingly poor, fair, good, or excellent supplies of breast milk. Colostrum was manually expressed from the breasts of 15 women, 4 of whom were multiparas and 11 of whom were primiparas. Five out of the 15 had a poor amount of colostrum (1 c.c. or less); 4 had fair amounts of colostrum (1 to 2 c.c.); 4 had an average or good amount (2 to 5 c.c.); and 2 had an excess amount (30 c.c.). In all but 3 cases the amount of colostrum obtained conformed with the individual's supply of breast milk during the first ten post-partum days. The three exceptions were: In two individuals the amount of colostrum drawn by manual expression was poor. Both these individuals during their first ten post-partum days had fair supplies of breast milk. The third gave an average amount of colostrum but produced a very good amount of breast milk. Further investigation is necessary before forming any definite conclusions.

gave two conflicting reactions. In these instances either one sample gave one reaction at one time and a different reaction at another time, or two different colostrum specimens gave unlike results when used at the same time in the same individual. Thirty-three patients showed definite nonpregnant reaction.

There were 48 cases of pregnancy from thirty-six to forty-three weeks' gestation. Twenty-two indicated pregnancy, 13 of these definitely and 9 with weak pregnancy reactions. Three cases had opposite reactions, using two different colostrum samples in the same patient at the same time. The remaining 23 cases were definite nonpregnant reactions.

In this group of 164 known pregnant women, 13 cases with conflicting results were discarded. There were 151 cases considered in the calculation. Eighty-two of the 151 gave pregnant reactions making the percentage of accuracy for the entire group 54.30. For the group (No. 40) of early gestations 25 cases out of 38 gave pregnant reactions (2 were discarded because of conflicting results) making the percentage of accuracy 65.78.

Eighty-four patients known to be nonpregnant were tested. Seventy-one of this number gave definite nonpregnant reactions. Three cases gave conflicting results. Ten cases indicated pregnancy either by definite (4) or by weak reactions (6). In computing the results, three conflicting cases were discarded, making a total of 81 cases. Seventy-one cases out of the 81 cases were correctly diagnosed nonpregnant, making the percentage of accuracy 87.65.

TABLE V. KNOWN PREGNANT AND KNOWN NONPREGNANT GROUPS TESTED

<i>Known pregnant 164 tested:</i>	
<i>Early months' gestation (27 from 4-12 weeks)—40 tested</i>	
25 indicated pregnancy (16 gave no reaction and 9 gave weak pregnancy reaction)	
*2 gave opposite reactions	
13 showed nonpregnant reactions	
<i>16 to 36 weeks' gestation—76 tested</i>	
35 indicated pregnancy (23 gave no reaction and 12 gave weak pregnancy reaction)	
*8 gave opposite reactions	
33 showed nonpregnant reactions	
<i>36 to 43 weeks' gestation—48 tested</i>	
22 indicated pregnancy (13 gave no reaction and 9 gave weak pregnancy reaction)	
*3 gave opposite reactions	
23 showed nonpregnant reactions	
<i>Summary:</i> 164 minus *13 leaves 151 cases considered in calculation.	
82 cases correct out of 151, or 54.30 per cent of accuracy, for entire group.	
28 cases correct out of 38, or 65.78 per cent accuracy, for group of early gestation.	
<i>Known nonpregnant 84 tested:</i>	
71 cases non-pregnant reactions	
*3 cases gave opposite reactions	
10 cases indicated pregnancy (4 gave pregnant reactions and 6 gave weak pregnancy reactions)	
<i>Summary:</i> 84 minus *3 leaves 81 cases considered in calculation	
71 cases correct out of 81, or 87.65 percentage of accuracy, for this group	

*Cases with opposite or uninterpreted reactions. Not considered in calculations.

taken into consideration. In the series, however, there were as many incorrect reactions from the use of sterile, filtered specimens as from the use of unfiltered samples.

There appeared to be no anterior pituitary hormone of pregnancy though this was not proved. A quantitative Aschheim-Zondek test showed no evidence of corpora hemorrhagica in four mice. Two rabbits were injected twice intravenously at twenty-four-hour intervals with 8 c.c. of colostrum and saline mixture. One rabbit showed corpora hemorrhagica in the left ovary at the end of forty-eight hours. Unfortunately, this rabbit had not been opened and examined previous to the injections. The other rabbit was opened and proved to be nonpregnant before the injection. This rabbit showed no change in the ovaries at the end of forty-eight hours. An interesting observation was the development of enlarging wheals and fiery-red areolas when approximately one-fiftieth cubic centimeter of colostrum mixture was injected intradermally in three rabbits. One of the three rabbits was pregnant.

All the patients in this series were questioned regarding skin sensitivity. They were checked with merthiolate and saline controls as mentioned. Sixteen patients were found to have a skin sensitivity. Three women were sensitive to the merthiolate control and 6 patients gave areola reactions to the saline control. Two of these cases sensitive to the controls had skin rash or sensitivity. Nine of the above 16 women with skin sensitivity had incorrect reactions with this skin test. No more skin sensitivity was found in the blondes and redheads than in the brunettes.

TABLE IV. SKIN SENSITIVITY

16 patients had skin sensitivity
3 patients sensitive to merthiolate (out of 89)
6 patients sensitive to saline (out of 248)
9 of the 16 patients gave incorrect reactions to the colostrum

In the majority of the known pregnant cases, it was necessary to make the final reading at sixty minutes in order to obtain the correct result. The intensity of reaction in the known nonpregnant women was usually greatest at ten minutes. In many of these cases the intensity of reaction diminished from this time on, but always persisted for at least sixty minutes.

Whenever the skin-injection was made subcutaneously instead of intracutaneously the reaction was either less intense or entirely negative. There was no success in correctly interpreting the reaction in exceptionally dark-skinned Negroes.

There were 164 known pregnant women tested (Table V). Forty of these were in the early months (within sixteen weeks) of gestation. Of this number, 27 were from four to twelve weeks pregnant. Twenty-five of the 40 cases indicated pregnant reactions, i.e., 16 gave no reaction and 9 gave a weak pregnancy reaction. Two of the 40 cases gave conflicting or opposite reactions. Here two different colostrum specimens were used simultaneously in the same individual. Thirteen of the 40 cases showed definite nonpregnant reactions.

From the sixteenth to the thirty-sixth week of gestation there were 76 patients tested. Thirty-five of these indicated pregnancy either with definite (23) or weak pregnant reactions (12). Eight of the 76 cases

2. There seems to be a difference either in potency in individual colostrum samples or a periodic change in individual sensitivity.
3. Skin sensitivity seems to play a part in false or incorrect reactions.
4. Further work should be done on the hormonal content of colostrum.

We would like to express our appreciation to Dr. Freeland of the Chemistry Department at Presbyterian Hospital for his work in checking the total protein and nonprotein nitrogen values of the colostrum samples, also to Dr. Bernice Rhodes of the Department of Bacteriology.

Discussion

DR. FRED H. FALLS.—A discussion of a paper of this kind is a discussion of the interpretation put on reactions that are new.

When we first attempted to find a skin reaction in pregnancy back in 1916, we were stimulated by a paper that was written by Engelhorn and Wentz in Germany. These authors claimed that the placenta contained material in the form of protein which when injected into the skin would give a positive skin reaction. This was based on the theory of Abderhalden that there were ferments mobilized against the placenta protein and that these ferments attacked the placenta protein and produced this reaction. At the same time that Engelhorn and Wentz were working on that reaction, we were working at the University of Illinois. Bartlett and I got only 60 per cent accuracy. Later on I asked Dr. Freda to repeat that work. After working a half year Dr. Freda got the same type of result that we got in 1916. We then started to work on the colostrum skin test. The test from the start seemed to have much more promise than did the placenta protein; in fact, it was so good that we doubted its value. We thought there was something wrong. It was not until we began to get an occasional false reaction that I felt we really had a biologic test. I know of no biologic test that is 100 per cent positive. Since we came out with our first paper on the subject we have continued with the test. We have supplied material to other workers and some of them have reported good results, and some not too good. One of these at the University of Oregon reported 95 per cent positive reactions. At Duke University very good results are reported, around 90 per cent. At George Washington University in Washington they report excellent results. In Little Rock, Ark., Dr. Rogers has done about 60 tests, and reports 90 per cent positive reactions including four ectopics which were proved by operation. At the Cook County Hospital we had the residents employ the test in suspected cases of ectopic pregnancy. We have 35 suspected ectopic pregnancies of which 30 were proved by operation. The reaction was correct in both cases.

It is hard to see why Drs. Allen and Donaldson do not have somewhat comparable results to those we have gotten.

The question of infection is raised by this paper. We have not found that it is a factor in any of our cases. We have not had a single abscess or any reaction where the skin had to be incised. Whether there is something in the technique that led to the rather high percentage of infections or whether the icebox got warm or what not, it is hard to say. At least, we have not found that particular effect in the preparations we have used.

We, of course, recognize very definitely the question of reading the reaction in the dark-skinned Negroes, and in the cases we have at the Cook County and Research Hospitals, where there are many Negroes, we found it was difficult to read the test but not at all impossible. If you get the arm in a good light and give the patient sufficient time to develop a reaction, as Dr. Donaldson did, it is not impossible to read the reaction, either pregnant or nonpregnant, although it is not as easy as in the blonde skin.

Included in the above report is a series of 48 known pregnant and known nonpregnant cases tested with a "pooled" colostrum sample prepared by Dr. Freda. Using this colostrum these 48 cases showed 11 out of 12 correct in the nonpregnant group, or 91.66 per cent of accuracy; and 16 out of 36 correct in the pregnant group, or 44.44 per cent of accuracy.

Six patients were suspected to have ectopic pregnancies. Three of these 6 cases were proved by operation to be ectopic gestations. The colostrum intradermal test was correct in 2 of the 3 cases. The fourth case gave a pregnant reaction to the skin test and a positive Aschheim-Zondek test but operation showed an orange-sized corpus luteum cyst of the left ovary. In the fifth case the patient had an early incomplete abortion. The pregnant reaction was correct. In the last case the skin test gave a nonpregnant reaction and the Aschheim-Zondek test was negative. This patient had a ruptured inflammatory cyst with free blood in the abdomen.

One patient was subjected to the test for 13 consecutive days from the onset of the menses until seven days postmenstrually. The general reaction pattern was nonpregnancy for the first one-half of the menstrual period and pregnancy for the last one-half of the period until four days after the menstrual period ended. From this time on the reaction was nonpregnancy. Ten patients were tested either during or shortly following the period. Seven of the 10 cases gave correct nonpregnant reactions. Three cases gave incorrect pregnancy reactions. One regularly menstruating woman without any previous skin sensitivity gave mild nonpregnancy reactions using two different colostrum samples at the same time. Since these injections, this individual has had 5 menstrual periods. Each time for five days premenstrually, she has developed at the former sites of the injection bright-red pruritic areolas. This phenomenon has not been noticed in any other case. Seven days following her test she developed pityriasis rosea which has persisted to the present date.

Nine women in the menopause were tested. All but one of these gave nonpregnancy reactions. This patient gave first a pregnancy reaction, then one month later a nonpregnancy reaction when a different colostrum sample was used.

There were 7 women tested when six weeks post partum. All but 2 of these patients showed nonpregnant reactions. One was tested with two colostrum samples and gave both a pregnancy and a weak pregnancy reaction.

In the entire series there were 7 cases which first gave one type reaction, then one to two months later gave another type reaction. One patient who had given pregnancy reactions on two previous occasions gave a nonpregnancy reaction, using the same colostrum sample on the day she aborted.

Four patients in the midpregnancy periods were tested every three days for five times, using the same colostrum sample. In all cases the intensity of reactions varied.

The following conclusions have been drawn from the above study:

1. This series gave a lower index of percentage of accuracy in both pregnant and nonpregnant groups than that of the original investigators. The nonpregnant group gave the higher degree of accuracy.

CLINICAL PELVIMETRY AND PELVIC PALPATION AS A BASIS FOR MORPHOLOGIC CLASSIFICATION OF THE OBSTETRIC PELVIS*

A Preliminary Report

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CLINICAL pelvimetry as ordinarily practiced and interpreted has provided criteria for classification of pelvis into normal and contracted types on the basis of size. Our roentgenographic studies of 1,500 obstetric pelvis in the stereoscope have shown that virtually all normal and contracted pelvis can be classified on a morphologic basis.

Our radiographic experience and a large number of dried pelvis in the Cornell collection, have shown that the size of certain diameters and structural characteristics are indicative of the gynecoid, android, anthropoid and platypelloid types of Caldwell and Moloy.¹ If this is so when dried pelvis or radiograms are studied under direct vision, then it is likely that clinical mensuration and vaginal palpation can provide information for morphologic classification of the obstetric pelvis. The purpose of this communication is to ascertain whether such an approach is practical and feasible.

Present Study

A group of 100 patients in the Woman's Clinic were subjected to clinical pelvimetry as will be described below, and also to a careful pelvic palpation by vaginal examination. The character of the sacral curva-

TABLE I. MORPHOLOGIC CHARACTERISTICS USUALLY ASSOCIATED WITH THE PELVIC TYPES

SEGMENT	GYNECOID	MORPHOLOGIC PELVIC TYPE		PLATYPELOID
		ANDROID	ANTHROPOID	
Anterior:				
Internal-spinous diameter	Average	Narrow	Narrow	Wide
Spines	Average	Sharp	Blunt	Average
Forepelvis	Average	Pointed	Pointed	Average
Pubic arch	Average	Narrow	Narrow	Average
Posterior:				
Sacrosciatic notch	Average	Narrow	Wide	Average
Curvature of sacrum	Average	Straight	Average	Average
Tip of sacrum	Average	Angulated forward	Average	Average

*This study has been conducted under a grant from the Bostwick Fund established by Mr. and Mrs. Dunbar Bostwick and friends.

†Dr. Steele died June 18, 1942.

It is interesting that the authors got 87 per cent correct reactions in the non-pregnant and only 54 per cent in the pregnant. Our percentage in the pregnant was not quite so good as in the nonpregnant. In the first series it was 98 per cent in the nonpregnant and 96 per cent in the pregnant. We did not know just what that meant.

The plan of pooling the colostrum we think is good. We recognize that by putting in several types we get a more even colostrum sample.

I think it is unfortunate that this test was given so much publicity in Detroit, the inference being that all that was necessary was to inject colostrum with a tuberculin syringe and within a few minutes one had the right answer. That is not true. There are several factors that have to be very carefully observed.

In many cases the reactions are done just as soon as a woman misses a period and that is why so many of them are called nonpregnant. We have not seen anything in the last year that would make us think this reaction will not stand the test of time. If we were the only ones getting positive results with everybody else getting bad results, then we would be skeptical. The fact that in good places they are getting good results makes us think that the time is coming when everyone will use the test for what it is worth.

DR. A. C. IVY.—I wonder if any studies have been made regarding the effect of merthiolate on the concentration and also regarding the time of contact of the colostrum with the merthiolate plus its exposure to light?

DR. EDWARD ALLEN.—We were almost as disappointed as Dr. Falls that our results were not a higher percentage of active reactions. Dr. Donaldson consulted with Dr. Freda many times to see if our technique was right. One patient had a recurrent flare-up of the wheal at each menstrual period. This brings up the interesting speculation of what happens in the glandular elements during that phase.

We feel very definitely that more work should be done on this interesting problem.

DR. DONALDSON (closing).—In my opinion the interpretation of the reaction is important. In the original article we stated that within the first six weeks of pregnancy and toward the last two weeks of pregnancy in 80 per cent of the cases, there was a weak pregnancy reaction. I think the real difficulty perhaps is in determining whether there is a weak pregnancy reaction or a non-pregnancy reaction.

In answer to Dr. Ivy, I believe Dr. Falls and Dr. Freda thought there might be some influence from the merthiolate. We have discontinued using it as a preservative. Standing in the sunlight may likewise have had some effect.

Kahanpwa, V.: Uterine Rupture After Previous Cesarean Section, *Acta obst. et gynec. Scandinav.* 21: 52, 1941.

Five cases of rupture of the uterus following cesarean section are reported by the author. In two instances the rupture took place during pregnancy and in the remaining three, the accident occurred during labor. One of the mothers and four of the babies died. An analysis of these cases leads the author to insist that when cesarean section is performed, the incision be made exactly in the midline and low down if possible, completely within the isthmus. Women who have had cesarean sections must be carefully observed during subsequent pregnancies and sent to a hospital at the onset of labor.

J. P. GREENHILL



Fig. 2.—The transverse (1), anterior and posterior transverse (2 and 3), and the anterior and posterior sagittal diameters (4 and 5), govern the conformation of the inlet of the true pelvis. Within limitations, these diameters also control the size of the false pelvis. The external diameters of the latter can be measured as shown in Fig. 3.

POSTERIOR SEGMENT

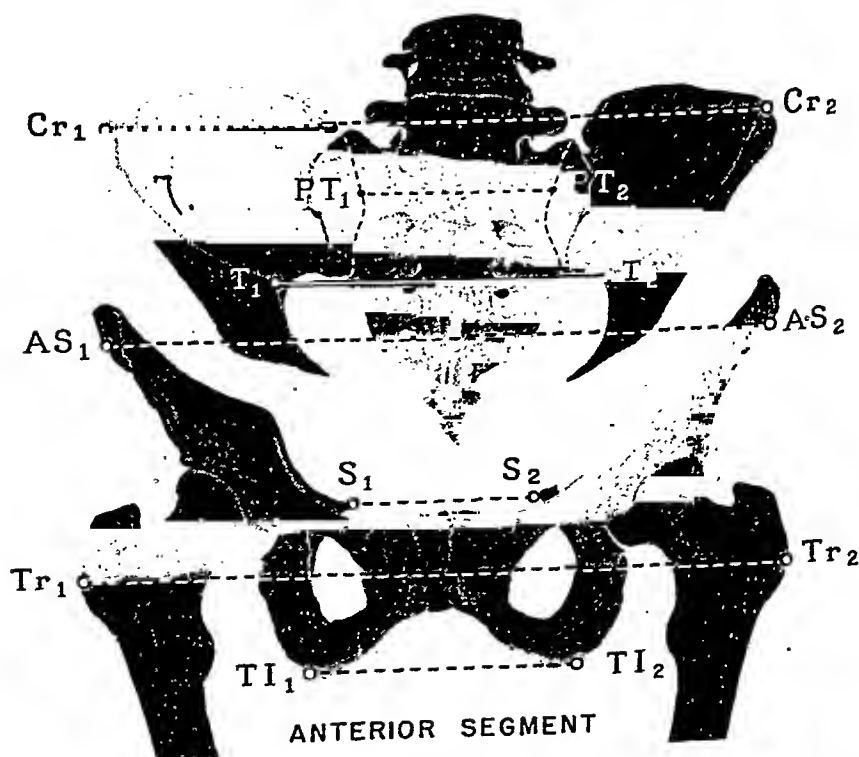


Fig. 3.—External diameters of anterior and posterior segments of the pelvis; AS₁-AS₂ between anterior superior spines, Cr₁-Cr₂ between the crests, Tr₁-Tr₂ intertrochanteric and PT₁-PT₂ the posterior transverse, or tuber ili diameter, which can be measured as shown in Fig. 4. The interspinous S₁-S₂ and Tuber Ischii TI₁-TI₂ diameters are also shown.

ture, the sacrosciatic notch, spines, pointing in the forepelvis, etc., was ascertained, as these vary with the type of pelvis, as Caldwell and Moloy² have emphasized and as shown in Table I. Each pelvis was then classified according to the individual morphology of each anterior and posterior segment, making 200 segments for consideration. Consideration of the pelvis in segments provides for a combination of these so that pure and mixed forms are recognized. This is essential, for about 50 per cent of pelvises constitute either group. As is the practice with roentgenologists and anatomists, the conformation of the pelvic inlet provides the key to classification. The features of the midpelvis and outlet are included because of their obstetric significance. The problem has been to discover whether clinical pelvimetry and vaginal palpation prop-

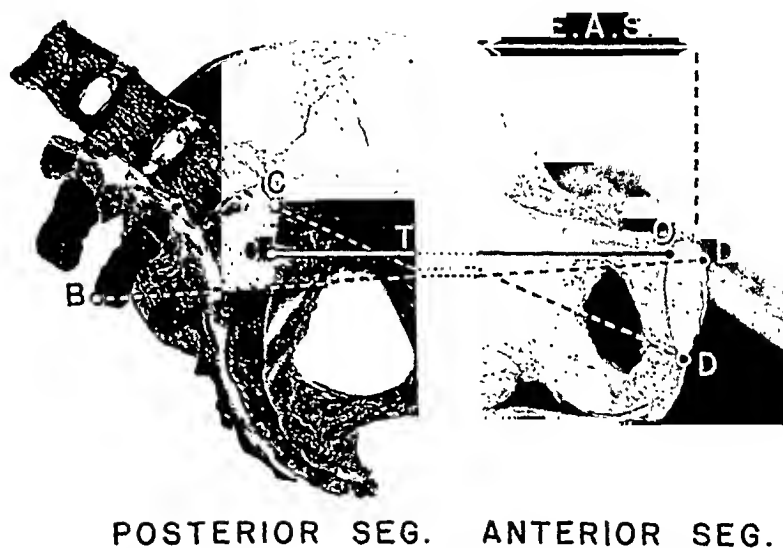


Fig. 1.—Showing the obstetric conjugate (CO) in the plane of the ileopectineal lines; the diagonal conjugate (CD), and the external conjugate (ED) and the external sagittal diameter ($E.A.S.$). A perpendicular to CO , in the coronal plane of the transverse diameter of the inlet, passing through the base of the ischial spines, divides the pelvis into anterior and posterior segments.

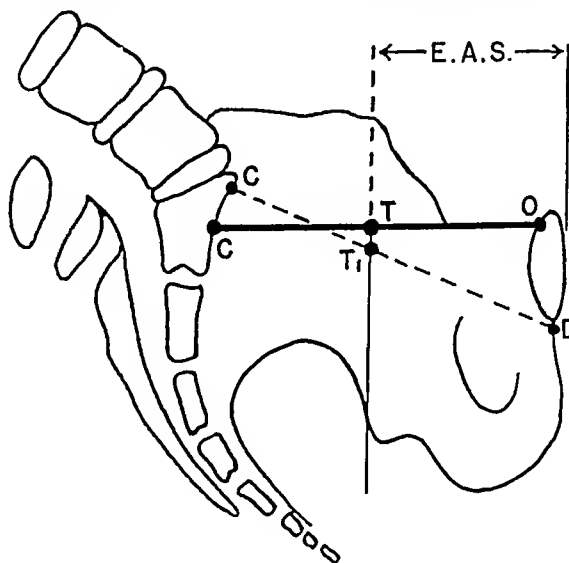
erly performed, interpreted and correlated, will provide for classification of the pelvic inlet on morphologic grounds.

The same patients were examined radiographically, using the combined isometric and stereoscopic technique of Steele and Javert,³ and the pelvis was classified according to segments. The x-ray diagnosis of pelvic type was used as the control for the clinical diagnosis. The clinical and radiographic studies were conducted independently, and the results were evaluated by a disinterested coworker.

Before comparing the data, certain principles require brief consideration. Fig. 1 shows the obstetric conjugate (CO) as the anteroposterior diameter of the inlet in the plane of the ileopectineal lines. A perpendicular to this diameter placed in the coronal plane of the transverse

The intercrural diameter gives an approximate idea of the transverse diameter of the inlet. The sum of the interspinous and intercrural diameters divided by 4 provides a numerical value.

A new diameter, the external anterior sagittal diameter, is shown in Fig. 1. It is difficult to measure accurately this diameter clinically. It was measured in a large number of radiographic films of various pelves and an average value of 7.0 cm. was obtained (± 0.75 cm.) for the four



$$C.D. - E.A.S. (7 \text{ cm.}) = C.T.$$

Fig. 5.—Clinical determination of the posterior sagittal diameter (C-T) of the inlet.

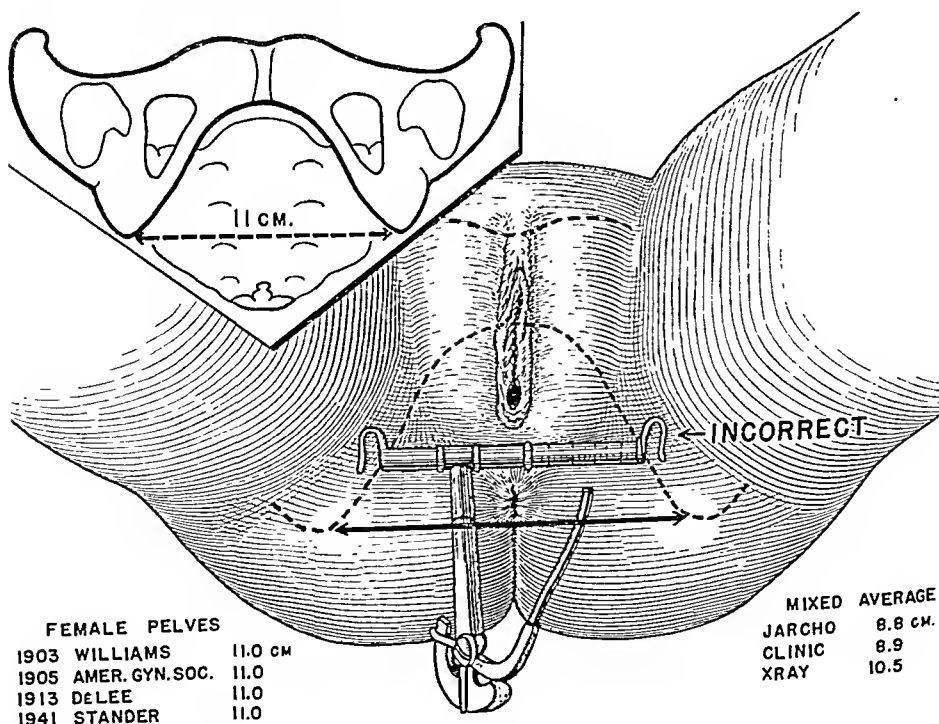


Fig. 6.—Mensuration of the tuber ischii diameter.

diameter of the inlet traverses the interspinous diameter as well as the diameter between the iliac crests in the region of the anterior superior spines. Accordingly, the entire pelvis is divided into anterior and posterior segments. The diameters and morphology of each segment have variations which can be detected clinically and these provide for classification of the obstetric pelvis on a morphologic basis.

Fig. 2 illustrates the diameters of the pelvic inlet when the pelvis is divided into its anterior and posterior segments. The size of the diameters of the true inlet obviously control the size of the diameters of the false inlet within certain limitations. Therefore, mensuration of the diameters between the anterior superior spines, the crests, the trochanters, and the posterior superior spines, shown in Fig. 3, and external and internal conjugates shown in Fig. 1, should provide an indirect index of pelvic size for purposes of classification.

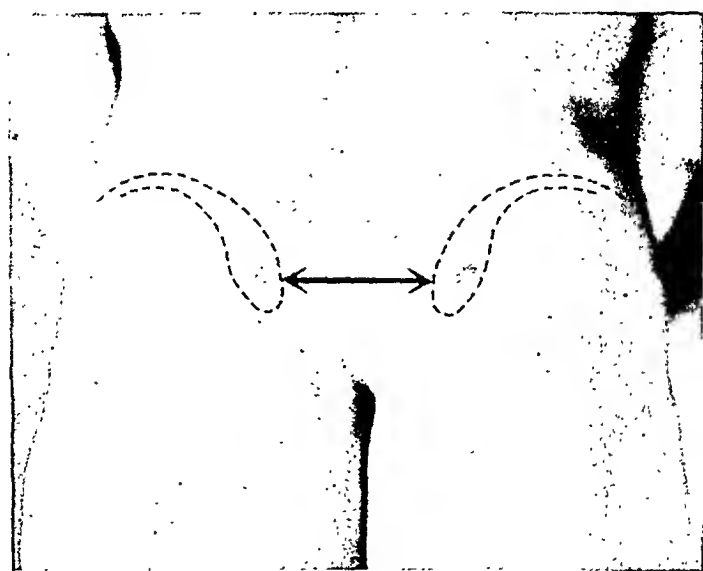


Fig. 4.—The posterior transverse diameter, between the bony prominences in the rhomboid, can be measured with a small Williams' pelvimeter.

The posterior transverse diameter (PT_1 - PT_2) recently described by Steele and Javert,⁴ and shown in Fig. 3, can be measured clinically in the rhomboid as indicated in Fig. 4. The average measurement for this diameter in 69 dried pelvis was 5.3 cm. for android pelvis, and 7.1 cm. for the gynecoid types. Therefore, when narrowed, it may be indicative of the android pelvis. Values obtained clinically are shown in Table II. These are usually equal to or slightly larger than the radiographic measurement.

The anterior transverse diameter also recently described by Steele and Javert³ assists in detecting narrowing in the anterior segment, or forepelvis. The distance between the anterior superior spines and the trochanters, provides approximate index of this diameter in the various morphologic types, and serves to detect narrowing of the forepelvis as does vaginal palpation.

for the tuber ischii diameter. Moreover, in addition to inaccurate measurement, sufficient consideration for soft parts has not been made, in this, the fattest region of the body.

TABLE III. CLASSIFICATION OF 100 Pelves BY CLINICAL AND MORPHOLOGIC STANDARDS

CLINICAL	GYNECOID	ANDROID	ANTHROPOID	PLATYPEL- LOID
Normal	45	12	13	6
Generally contracted typical	3	9	0	1
Funnel typical	0	1	0	0
Simple flat	2	6	0	1
Rachitic flat	0	0	0	1
Total	50	28	13	9

A comparison of the clinical or etiologic classification with the morphologic types in the 100 patients is given in Table III. As is shown, 24 per cent of the pelvises showed clinical evidence of contraction, and of these, 16 or two-thirds, were android in type. The gynecoid and anthropoid pelvises were nearly always regarded as "normal."

The percentage of accuracy in the clinical attempt at morphologic classification of 200 segments of the pelvis is given in Table IV. The

TABLE IV. PERCENTAGE OF ACCURACY OF THE CLINICAL DIAGNOSIS OF 200 ANTERIOR AND POSTERIOR SEGMENTS AS CONTROLLED BY MORPHOLOGY IN THE STEREOSCOPE

	GYNECOID	ANDROID	ANTHROPOID	PLATYPEL- LOID
Posterior Segment:				
Correct	82	84	62	10
Incorrect	18	16	38	90
Anterior Segment:				
Correct	71	54	60	43
Incorrect	29	46	40	57

gynecoid and android posterior segments were accurately diagnosed in about 80 per cent, which is satisfactory, since over three-fourths of all pelvises constitute these two types. Furthermore, clinical recognition of the android pelvis which has an unfavorable obstetrical prognosis is regarded as a true accomplishment. The poorer results in the platypelloid and anthropoid groups were caused by confusion with the gynecoid and android types. From the standpoint of size, such an error is not serious. In general, the pure forms were diagnosed more readily than the mixed types. The chief cause of error was found to be due to variations in size and in differentiating the gynecoid and platypelloid pelvises. For example, an android pelvis sometimes proved to be a small gynecoid pelvis and vice versa, or if large, was usually classified as anthropoid or gynecoid.

The experience gained from a large study (1,500) of pelvises by roentgenographic means has disclosed agreement and disagreement with the morphologic classification of Caldwell and Moloy,² DeLee,⁷ Stander,⁸ Thoms,^{6, 9} and Williams¹⁰ as summarized in Table V. Caldwell and Moloy (1942) have agreed to the inclusion of their gynecoid pelvis with the female oval or brachypellie types of other classifications. As indicated

parent types. This value when subtracted from the diagonal conjugate, gives the posterior sagittal diameter of the posterior segment as indicated in Fig. 5 and Table II. Its greatest value lies in the detection of the short posterior sagittal diameter in the android and the longer posterior sagittal diameter in the anthropoid pelvis.

The diagonal conjugate can be measured more easily by placing the fist of an assistant, or a 4-inch roll in the lumbosacral curvature. This serves to level off the superior strait and makes the promontory more accessible.

Average values obtained clinically for the various diameters, and the morphologic characteristics of the anterior and posterior segment, on vaginal palpation, from inlet to outlet, according to morphologic pelvic type (as determined clinically and roentgenographically), are shown in Tables I and II. Only the external and internal diameters giving in-

TABLE II. AVERAGE DIAMETERS BASED ON CLINICAL PELVIMETRY OF 100 CASES

	MORPHOLOGIC TYPE			
	GYNECOID	ANDROID	ANTHROPOID	PLATYPELOID
<i>Anterior Segment:</i>				
*Interspinous diameter	25.5	23.5	25	27
*Intertrochanteric	32	28	30	31.5
Tuber ischii diameter	11	10	10	11.25
<i>Posterior Segment:</i>				
*Intercristal	27	27	27	28
*Posterior transverse	8.5	7	8	8.5
<i>A-P Diameters (pure types):</i>				
Baudelocques	19.5	19	20	19
C. D.	12.25	11.5	13	11.75
<i>Sagittal Diameters:</i>				
*Posterior (internal)	5	3.75	6	4.5

*Only these diameters are utilized for morphologic classification of pelvis.

formation as to the pelvic inlet are utilized for morphologic classification in accordance with the recent views presented by Steele and Javert⁴ in their discussion of roentgenographic classification of the obstetric pelvis.

Morphology and mensuration of the midpelvis and outlet are of value in a confirmatory manner. If the pelvic inlet is android and the sacrosciatic notch is narrow, this is confirmatory. Likewise, if the inlet is android and the transverse diameter is only 9 cm., it is also confirmatory. However, if the sacrosciatic notch and outlet are wide, the inlet may be still android. Therefore, care in interpretation and correlation of data is essential because of the multiple variations that are encountered. That is the reason the brim has been chosen as the key to classification in order to avoid a cumbersome situation.

For completeness, it seems necessary to point out that most obstetricians measure the tuber ischii diameter too short. Most textbooks indicate that this diameter measures 11 cm., yet illustrate the use of Thom's pelvimeter at a level *above* the anal orifice, as shown in Fig. 6, which is too high on the pubic arch. Using this technique, Jarcho⁵ and our clinic have obtained average values of only 8.8 and 8.9 cm., respectively, for this diameter in a group of mixed pelvis, whereas, a similar group of patients studied radiographically showed an average value of 10.5 cm.,

over, such a procedure aids in the detection of contracted pelves and these can then be subjected to further roentgenographic study, thereby increasing accuracy of pelvic classification.

Most of the contracted pelves were android, platypelloid or small gynecoid in type. The so-called "normal" pelvis of the gynecoid or anthropoid variety. While adequacy in size occasionally placed the android or platypelloid pelves into the "normal" group.

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HYPERTENSION AND PREGNANCY*

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ELEVATION of blood pressure above the average limits of normal is the most significant symptom of the toxemias of pregnancy. In fact, hypertension is present so consistently in the majority of diseases which are called toxemias of pregnancy that the term "hypertensive disease of pregnancy" would perhaps be more descriptive of them than is the term "toxemias of pregnancy." Hypertensive disease complicating pregnancy would then include chronic vascular and renal disease present prior to gestation, which is not a disease peculiar to pregnancy, and acute hypertensive diseases of pregnancy (pre-eclampsia and eclampsia), which are dependent on, and peculiar to, the pregnant state.

There is a notable difference between chronic vascular and renal disease which is present prior to pregnancy and acute hypertensive disease arising during pregnancy. The former, which will be referred to as chronic hypertensive vascular disease, is characterized by more or less generalized sclerosis of the arterioles which may have been caused by toxemia in a previous pregnancy, by previous acute illness or by unknown factors; the latter, which will be referred to as acute hyperten-

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in Tables III and V, the rachitic and simple flat are more often android than platypelloid. The round or mesatipellic pelvis is probably gynecoid with anthropoid or vice versa. In general, contracted pelves are of the pure or mixed android variety. The authors do not disagree with the transverse or A. P. elliptical pelves of other classifications.

TABLE V. AUTHORS' AGREEMENT AND VARIATION WITH OTHER CLASSIFICATIONS

OTHER CLASSIFI- CATIONS	ROUND NORMAL MESATIPPELLIC	OVAL BRACHYPELLIC FEMALE .	TRIANGULAR FUNNEL ANDROID MALE GEN. CON. FUN. RACHITIC FLAT SIMPLE FLAT	NARROW, TRANSVERSE ELIPSE, PLATYPELLIC PLATYPELLOID	A. P. ELIPSE DOLICHOPELLIC ANTHROPOID, TRANSVERSELY CONTRACTED
	GYNECOID		Android or mixed	Platypelloid	Anthropoid
	FEMALE				
Authors 1942	Gynecoid or Anthropoid or vice versa	Gynecoid			

Routine x-ray examination of every pregnant woman, especially primiparous, has been advocated by Thoins and others. Such a program is very tenable when one compares the maternal and fetal morbidity due to syphilis (1 per cent in the Woman's Clinic) for which a serologic test is compulsory, with the clinical incidence of contracted pelves (15 per cent). This argument is made more forceful by the recent report of Steele and Javert⁴ who found that the incidence of contracted pelves is nearer 30 per cent when x-ray pelvimetry is employed. Therefore, routine radiographic study appears to be a prerequisite to sound obstetrical practice. It is probable that Public Health Authorities will ultimately realize this and insist on at least one radiographic examination in the lifetime of every childbearing woman, using a suitable technique. Until such a time, we believe that the principles outlined above will aid in the clinical classification of pelves with added accuracy and will also serve as a basis for selection of certain patients for roentgenographic study.

Summary and Conclusions

A clinical approach to the morphologic classification of pelves is presented. Mensuration is employed for the determination of size and vaginal palpation is utilized for the detection of morphologic characteristics.

A perpendicular line to the inlet divides the entire pelvis into its anterior and posterior segments, each having certain diameters and morphologic characteristics. These may be employed for classification of the obstetric pelvis on a morphologic basis. The diameters of the true inlet control the size of the false inlet within certain limitations and the diameters of the latter can be measured by external pelvimetry. Experience has shown that mensuration alone is not always an accurate index of morphology. However, it has been found in a study of 100 patients (200 segments) that clinical mensuration of certain diameters and vaginal palpation of morphology of the brim, midpelvis and outlet, provides sufficient data to classify about 75 per cent of pelves. More-

Minor changes, then, in the caliber of the arterioles owing to generalized arteriosclerosis in chronic hypertensive disease or to generalized vascular spasm in acute hypertensive disease complicating pregnancy increase the back pressure in the arteries, which stimulates the minute volume output of the heart and elevates the blood pressure. The height of the blood pressure in the presence of adequate cardiac output and normal blood volume is then an index of the degree or intensity of the peripheral resistance caused either by arteriolar sclerosis or spasm, as the case may be.

The lability of the blood pressure and its dependence on cardiac output and peripheral resistance should be kept in mind in the management of patients with severe chronic cardiovascular disease with or without superimposed toxemia. Following parturition, such patients may have a sudden drop in blood pressure, so-called vascular collapse, owing partly to suddenly lowered peripheral resistance and possibly partly to cardiac decompensation.

The concept of the presence of spasm of the arterioles as the predominant factor in the production of hypertension in the acute toxemias of pregnancy has been generally accepted. Various hypotheses have been advanced concerning the cause or causes of this arteriolar spasm, but none have been proved to the satisfaction of a majority of observers.

The classification of the toxemias of pregnancy adopted by the American Committee on Maternal Welfare two years ago is predicated on the acceptance of hypertensive disease or hypertension as the common denominator of the following two large groups: (1) chronic vascular disease or renal disease with hypertension, and (2) acute hypertensive toxemias. Other conditions, such as vomiting of pregnancy, nephrosis

TABLE I. CLASSIFICATION OF TOXEMIAS OF PREGNANCY

Group A. Disease not peculiar to pregnancy
I. Hypertensive disease (hypertensive cardiovascular disease)
a. Benign (essential, mild, severe)
b. Malignant
II. Renal disease
a. Chronic vascular nephritis or nephrosclerosis
b. Glomerulonephritis
1. Acute
2. Chronic
c. Nephrosis
1. Acute
2. Chronic
d. Other forms of severe renal disease
Group B. Disease dependent on, or peculiar to, pregnancy
I. Pre-eclampsia
a. Mild
b. Severe
II. Eclampsia
a. Convulsive
b. Nonconvulsive (that is, coma with post-mortem findings typical of eclampsia)
Group C. Vomiting of pregnancy
Group D. Unclassified toxemias

sive disease, arises during pregnancy and is characterized by an acute vasospasm affecting the arterioles of a previously "normal" vascular system. This distinction will be referred to later when the management of the two conditions is considered.

Inasmuch as the disease in both instances affects primarily the arterioles, it is pertinent to recall, briefly, the role of the arterioles in the maintenance of blood pressure and the production of hypertension. When a fluid such as blood is pumped through a series of tubes such as the vascular system, the pressure necessary to propel the fluid at a given rate depends on several factors: the force of the pump, the rate of pumping, the volume and viscosity of the fluid, the size of the tube, and the nature of its lining. In terms of physiology, this would depend on the minute volume output of the heart, the volume and viscosity of the blood, the elasticity of the arteries and the peripheral resistance of the arterioles.

It will be recalled that the minute volume of the heart is based on the number of contractions per minute and the amount of blood expelled at each contraction. Either or both may be increased but do not cause constant hypertension, except perhaps in hyperthyroidism and in "effort syndrome." During normal pregnancy, there is an increase in blood volume but, as Dieckmann stated, there may be a relative or actual decrease in blood volume in acute hypertensive toxemias of pregnancy. These facts indicate that increase in blood volume is not a cause of the hypertension. Viscosity of the blood usually is unchanged in the initial stage of hypertension, although it is increased later when the toxemia becomes severe, and it then may be a factor in further increase of hypertension. The region served by the arterioles in the vascular tree is so great that these vessels contain a large portion of the volume of blood, so that decrease in their caliber owing to the sclerotic process in chronic hypertensive disease causes definite resistance to blood flow and increases the blood pressure in the larger arteries.

Acute toxemia of pregnancy is not accompanied by sclerosis of the arterioles. The sclerosis which may appear later is not yet present. What, then, causes hypertension in the acute toxemias of pregnancy? Contraction of arterioles is similar to the action of most other hollow muscular organs and occurs as a result of increase in muscle tone; dilatation follows lessening of tone. Contraction or spasm of arterioles which occurs in hypertensive toxemia may be caused by the neurogenic stimulation of the vasomotor center through the autonomic nerves, such as may occur in essential hypertension, but in all probability it is due to the angiogenic effect of a pressor substance circulating in the blood, which acts directly on the wall of the arteriole to produce contraction or spasm of the vessel. Similar spasm has been observed in the arterioles of the ocular retina and in the capillary loops of the nail fold in cases of toxemia.

complicates pregnancy the evidence of renal vascular involvement or nephrosclerosis predominates over other systemic vascular manifestations. In addition to hypertension, patients who have nephrosclerosis have albuminuria, usually of a moderate degree, commonly are unable to concentrate urine to a specific gravity of 1.022, often exhibit residual evidence of albuminuric retinitis, and, when the condition is advanced, are prone to have increased retention of nonprotein nitrogen in the blood. The highest incidence of intrauterine fetal deaths occurs in cases in which impairment of renal function is most severe.

Acute Hypertensive Disease (Pre-eclampsia and Eclampsia)

The entire syndrome of acute hypertensive disease of pregnancy (pre-eclampsia and eclampsia) develops in the course of a given pregnancy. In this sense it is distinct from chronic vascular renal disease which affects patients prior to pregnancy. Probably there is an underlying familial tendency toward hypertension among a majority of patients who have pre-eclamptic toxemia. Certainly, when acute pre-eclamptic toxemia is present it occurs most commonly in the latter part of the first pregnancy. Perhaps the patients are among the so-called hyper-reactors who respond in this fashion to the strain or, should one say, the stimulus of pregnancy.

Symptoms of acute hypertensive disease rarely become evident before the twenty-fourth week of gestation and commonly not before the ninth or tenth lunar months. Exceptions occur but these exceptions probably are often examples of previously undiagnosed mild chronic vascular disease with superimposed toxemia. The clinically descriptive terms, "mild" and "severe," are useful in designating the degree of severity of pre-eclampsia. The term, "low reserve kidney," fulfilled a useful purpose in emphasizing mild degrees of hypertensive disease in pregnancy. Follow-up studies in these cases indicate that in many cases chronic vascular disease develops and strongly suggests that the symptoms were due to a sensitive or hyperreactive vascular system rather than to low kidney reserve.

In cases in which the toxemia is mild, the systolic blood pressure is between 140 and 160 mm. and the diastolic blood pressure is between 90 and 100 mm.; the urine contains less than 0.6 Gm. of albumin per 100 c.c. and the edema is slight or undemonstrable. Usually, no changes are present in the retinal arteries. Severe pre-eclampsia develops in few cases and eclampsia in still fewer. However, there are as yet no certain clinical or laboratory methods which will distinguish potential eclampsia among cases of mild pre-eclampsia.

In cases of severe acute hypertensive disease the systolic blood pressure is usually more than 160 mm. after rest and the diastolic blood pressure is 100 mm. or higher. Relatively high diastolic blood pressure as compared with the systolic pressure indicates more intense "toxemia." The rise in systolic and diastolic blood pressures in toxemia of pregnancy is roughly on a 2:1 ratio. For example, a 50 mm. rise of systolic blood pressure from a basal level of, perhaps, 120 mm. to 170 mm. would indicate a probable 25 mm. rise of the diastolic pressure from, perhaps, 80 mm. to 105 mm. In such a case, with a systolic blood pressure of 170 mm. a diastolic rise of 30 mm. or more would be strongly suggestive of more intense arteriolar spasm. Ordinarily, more severe toxemia is associated with the passage of more than 0.6 Gm. of albumin

and other renal diseases not accompanied by hypertension, were included among the toxemias largely owing to custom and for want of a better arrangement. An unclassified heading was inserted to include those conditions, which, because of insufficient or inconclusive data, cannot be classified in the course of pregnancy or the puerperium.

A classification of the toxemias of pregnancy should be practical and usable (Table I). To be practical, it must be relatively brief. It must contain sufficient descriptive terms to be usable during the course of pregnancy and to be available for the collection of data for study and reference following the termination of pregnancy. For the purpose of defining the hypertensive toxemias of pregnancy, one is concerned chiefly with the main headings. A majority of the various subheadings were placed in the classification largely to permit more complete indexing.

Cardiovascular and Renal Disease

Chronic cardiovascular and renal diseases are classified as toxemias of pregnancy because they present an obstetric problem, since the underlying pathologic lesion or lesions of each which are present prior to pregnancy tend to be aggravated in the course of pregnancy prior to the twenty-fourth week, and they tend to produce symptoms, one or more of which simulate those of acute hypertensive disease (pre-eclampsia and eclampsia). The twenty-fourth week is arbitrarily selected as the dividing line between chronic vascular disease and acute hypertensive disease, because symptoms in the former group of conditions almost always become evident before the twenty-fourth week and symptoms of the latter commonly develop after the twenty-fourth week. A systolic blood pressure of 140 mm. of mercury and a diastolic blood pressure of 90 mm. or more are considered sufficient evidence on which to make a diagnosis of hypertensive toxemia. This rise in blood pressure may be accompanied by more or less albuminuria or edema or both. Exceptionally, blood pressures even below 140 mm. systolic and 90 mm. diastolic may indicate chronic vascular disease if accompanied by other conclusive evidence, such as retinal arteriolar changes or lowered renal function.

Symptoms and findings indicating the degree of severity of chronic vascular disease are more readily defined by use of the terms, "mild" and "severe." In general, the criteria of mild hypertension are the absence of marked vascular changes as indicated by a heart of essentially normal size, little if any change in the arterioles of the retina, a systolic blood pressure between 140 and 160 mm. of mercury, a diastolic blood pressure between 90 and 100 mm. after rest, and clinically normal renal function. In many of these cases the evidence of chronic hypertensive disease may have been inconclusive prior to pregnancy.

In cases of severe or advanced hypertension there is commonly found heart disease or enlargement; there are usually evident changes in the retinal vessels, persistence of systolic blood pressure of more than 160 mm. of mercury and of diastolic pressure of more than 100 mm. of mercury after rest and, occasionally, evidence of impaired renal function.

Renal Vascular Disease.—Chronic hypertensive disease is essentially a diffuse process affecting the arterioles of the entire body, and on a purely pathologic basis nephrosclerosis should be placed under this heading. However, in some cases in which chronic hypertensive disease

jury may occur in cases of acute hypertensive toxemia, but it is not likely, in its acute stage, to be accompanied by disturbances in function similar to those of nephrosclerosis.

Review of Cases

Two hundred and ninety-seven cases of toxemia of pregnancy (Table II) were observed at the Mayo Clinic in the ten years from 1932 to 1941, inclusive; during this time 5,207 labors were conducted, giving an incidence of hypertensive toxemias of 5.7 per cent. Eleven pregnancies were interrupted early because of severe chronic vascular or renal disease. Two hundred and eighty-six pregnancies were carried to or beyond the twenty-fourth week of gestation; 298 babies were born, including twelve pairs of twins. Following the classification described previously, there were 48 cases of chronic vascular disease, of which 28 were mild and 20 severe (in 11 of these 20 cases the pregnancy was interrupted early), 50 cases of chronic vascular disease with superimposed acute toxemia, of which 16 were mild and 34 severe, 158 cases of acute hypertensive disease, of which 72 were mild and 86 severe, 24 cases of eclampsia, 2 cases of nephritis with nephrosis, and 2 cases of pyelonephritis. In 13 cases the toxemia was unclassified. It is of interest to note that the disease was of the chronic hypertensive type in only 33 per cent of these cases. In 53 per cent the diagnosis was acute hypertensive disease and in 8 per cent it was eclampsia. The incidence of convulsive toxemia is higher than that reported by Irving (1.1 per cent) or by Plass (1.7 per cent). Nineteen, or 79.1 per cent, of the 24 patients who had eclampsia, had not received prenatal care while 95 per cent of all the patients had received prenatal care. If one were to count only the cases in which the patients received adequate prenatal care, the incidence of eclampsia is less than 2 per cent.

Eleven therapeutic abortions were performed because of severe chronic hypertensive disease, associated in at least 5 cases with nephrosclerosis. Practically all of the patients were referred by other physicians. The average age was between thirty-five and forty years and the group had an average of over two living babies. The average maximal blood pressure was about 190 mm. systolic and 120 mm. diastolic, measured in millimeters of mercury.

Study of the data in this series of 286 cases indicates that antepartum care was lacking or inadequate in many of the emergency admissions of patients who had severe pre-eclampsia and in approximately 80 per cent of the patients who had eclampsia. Cesarean section was the method of delivery in 5 per cent of the cases; toxemia was the primary indication in one of 14 patients on whom cesarean section was performed.

Management of Hypertensive Toxemias of Pregnancy

It is not the purpose of this paper to consider fully the management of this condition. Routine, periodic, antepartum care, care of good quality as well as quantity, with carefully recorded blood pressure readings has made possible the early detection and treatment of hypertensive toxemias of pregnancy and has lowered the incidence of eclampsia. It appears to have lowered also the incidence of severe, acute, hypertensive toxemia. Certainly, patients who have received adequate ante-

per 100 c.c. of urine. The concentrations of uric acid and sulfates are often increased in the blood, but there is usually no essential change in the nonprotein nitrogen of the blood or in the urea clearance. In most cases, edema is graded 2 or more on a basis of 1 to 4. Usually, acute hypertensive changes may be observed in the retinal arteries.

A study of the retinas in a series of cases previously reported indicated that all patients who had a systolic blood pressure of 200 mm. or more had evidence of acute changes in the retinal arterioles, most of which were severe; 90 per cent of the patients who had systolic blood pressure between 170 and 200 mm. had retinal changes, and only 52 per cent of those whose systolic blood pressure was less than 160 mm. had such changes, and these changes were predominantly mild. Thus, a progressive relationship was demonstrated between higher blood pressure and the more commonly encountered and severe changes in the retinal arterioles. Moreover, the degree and extent of the spasm of the retinal arterioles were usually directly proportional to the severity of the toxemia.

It is sometimes extremely difficult to decide whether hypertension and other symptoms are due to chronic vascular disease or to acute hypertensive toxemia. The former commonly occurs in multiparas who are more than thirty years of age, the latter among primiparas who are less than thirty years of age and who usually are less than twenty-five years of age. In many cases of chronic vascular disease, evidence of sclerosis or albuminuric retinitis may be demonstrable in the retinal arterioles; such retinal changes are not found in cases of acute toxemia unless this toxemia is superimposed on chronic diseases, in which case acute vascular spasm may also be observed. The widespread nature of vascular disease may cause sufficient renal injury to produce evidence of nephrosclerosis with lowered renal function; more or less renal in-

TABLE II. TYPES OF TOXEMIA OF PREGNANCY: INCIDENCE OF FETAL MORTALITY, 1932-1941 INCLUSIVE

TYPES OF TOXEMIA	NUMBER		FETAL DEATHS	
	MOTHERS	BABIES	NUMBER	PER CENT
Chronic vascular disease				
Mild	28	28	5	18
Severe	20*	20	14*	70
Chronic vascular disease with superimposed pre-eclampsia				
Mild	16	18	1	6
Severe	34†	36	10	28
Renal disease				
Nephritis with nephrosis	2	2	0	0
Pyelonephritis	2	2	1	50
Pre-eclampsia				
Mild	72	73	2	3
Severe	86	91	14	15
Eclampsia	24‡	26	12	46
Unclassified	13	13	1	8
Total	297	309§	60*	19
Less 11 therapeutic abortions	286	298	49	16

*11 therapeutic abortions

†1 maternal death—pulmonary embolus

‡3 maternal deaths; all were admitted in coma; 2 had pneumonia

§12 pairs of twins

Obviously, chronic vascular disease associated with pregnancy is a potentially serious complication. However, in some instances the vascular damage is slight and little change in blood pressure may occur in the course of pregnancy. Teel and others observed that many patients show an elevation of blood pressure early in pregnancy and then, owing to the physiologic lowering of blood pressure which commonly occurs between the eighth and thirty-second weeks in normal pregnancy, such patients with latent hypertension may not manifest any appreciable rise in blood pressure until late in pregnancy. If such a patient were first observed when the pressure is at a lower level, the later rise may be attributed incorrectly to pre-eclampsia. As a matter of fact, not a few patients with mild chronic vascular disease and some who have severe disease may pass through pregnancy without appreciable increase in blood pressure and with no superimposed toxemia.

For example, a primigravida, aged 38 years, at the thirtieth week of gestation was referred by her physician on account of hypertension. She gave a history of having been refused insurance five years previously because of hypertension. During her ten days' stay in the hospital her blood pressure varied between 140/90 and 160/110. No albumin was present in the urine. The concentration of serum sulfates was 3.9 Gm. per 100 c.c., that is, within normal limits. The retinal examination showed evidence of arteriosclerosis Grade I, but no evidence of vascular spasm. She was readmitted at the thirty-eighth week of pregnancy with a pressure of 150/90. Spontaneous onset of labor and delivery occurred a few days later. The infant weighed 2,490 Gm. and was living and well. The patient was dismissed to the care of her physician at the tenth day post partum, at which time her blood pressure was 140/90.

Excellent follow-up studies which have been made by Corwin and Herrick, Stander, Peekham and others indicate that an appreciable number of patients who have mild chronic or mild, acute, vascular disease later will show evidence of increased vascular injury and that a larger number of patients who have severe toxemia later will show evidence of chronic arterial disease. This effect of toxemia of pregnancy on the production or increase of vascular disease among women must be reckoned with, but there are numerous other factors which in progressive degree impinge upon or injure the vascular system with advancing years. Just as, for example, the man of thirty years who exhibits a blood pressure of 140/90 is often the subject of severe vascular disease at the age of forty or fifty years, so some women even without child-bearing may have severe hypertension. Various observers have reported that essential hypertension is a common disease in both sexes. Opinions differ concerning the relative frequency among the sexes, although the disease is possibly somewhat more common among women than among men. Fishberg stated that of 94 patients with chronic hypertension who were thirty or more years of age, 39 were men and 55 were women, a ratio of approximately 3:4. However, the life of the average woman

partum care require hospitalization for toxemia of pregnancy less frequently than do those who have received inadequate or no antepartum care.

The following generalizations in the management of toxemia of pregnancy deserve mention: (1) rest and sedation; (2) low salt diet; (3) ample protein and relatively low fat and carbohydrate diet; (4) increase of fluid intake unless oliguria persists; (5) hospitalization if possible before the process becomes severe; (6) shortening the course of the disease, when necessary, by the termination of pregnancy, and (7) conservatism in management of childbirth.

Space does not permit a consideration of the details of management. The fact is recognized that the number of women who suffer from chronic vascular disease subsequent to pre-eclampsia increases in proportion to the height and duration of the blood pressure. When the toxemia is severe, and when the patient fails to improve, or when, following improvement, there is a relapse, termination of pregnancy is indicated. The method employed to induce labor and the optional time for doing so depend on many factors, including age, parity, period of gestation, adequacy of the birth canal, condition of cervix and the severity and duration of the toxemia. Cesarean section is rarely employed for hypertensive toxemia, *per se*. If medical induction fails, we usually prefer to rupture the membranes artificially.

The treatment of eclampsia consists of measures to control convulsions. After this is accomplished, induction of labor is usually indicated. Cesarean section in cases of eclampsia, preferably under local anesthesia, is usually reserved for contracted pelvis and other obstetric indications.

Results

There were four maternal deaths (1.3 per cent) in the entire series of 297 cases. One mother who had severe acute hypertensive disease superimposed on chronic vascular disease died of pulmonary embolism eight days post partum. The remaining three all died of eclampsia; none had antepartum care, one was admitted four hours after delivery at home and all were comatose on admission and died without regaining consciousness; two had bronchopneumonia.

The total fetal mortality was 60 (19 per cent); omitting 11 therapeutic abortions, the corrected fetal mortality was 16 per cent, which is in general agreement with the incidence of fetal deaths in other series of cases of toxemia.

Comment

As mentioned previously, the acute toxic process not infrequently is superimposed on a previous chronic vascular lesion. Symptoms are produced which may be identical with those of acute toxemia so that if a history is not obtainable or if the patient is not observed prior to the twenty-fourth week of gestation, it may be impossible to decide whether the lesion is chronic or acute or both.

vascular disease is generally recognized. It is much less frequent in pre-eclampsia and eclampsia. Eleven cases of abruptio placentae were observed and in most of them the patients had chronic vascular disease. In a series of 58 cases of abruptio placentae reported from the Chicago Lying-In Hospital, 69 per cent of the patients had hypertension.⁴

Premature births frequently occur among patients with severe chronic hypertensive disease and the premature infants weigh less than the average for the same period of gestation; even at full term the babies weigh from 600 to 1,000 Gm. less than the average full-term infant. Prematurity and malnutrition plus the high incidence of abruptio placentae and stillbirths from other causes are accompanied by a high fetal mortality.

Schwarz, in 1923, and Adair, Hunt and Arnell, in 1936, pointed out a small but very important group of cases in which the exaggeration of the normal drop in blood pressure following delivery in toxemic patients proceeded to the point of grave shock. Schwarz reported a mortality of 38.5 per cent in his cases. In the series reported by Adair, Hunt and Arnell the extremely low maternal mortality was attributed to prompt recognition and vigorous treatment of the shock. In the absence of hemorrhage excessive surgical trauma or other probable causes of shock and in the presence of an acute strain (labor and delivery) on a vascular system overburdened by toxemia and hypertension, it appears probable that this shock is due to vascular collapse.

In the series of cases that we have reviewed, there were four cases of severe vascular collapse, in all of which the patients responded to prompt and repeated intravenous administration of fluids and one or more transfusions.

One should not be too dogmatic about the advice given to pregnant women with pre-existing chronic vascular disease. These patients should be individualized. Those observed in the first trimester with evidence of lowered renal function stand a poor chance of reaching full term with a live fetus; many fetuses die in utero and many are born prematurely.

There are two fundamental differences between man and woman. Man is stronger physically and his special function or role is the use of physical force, if necessary, to protect his family and community. Undeniably, woman's unique function is childbearing. When her pregnancy is complicated, a woman has the right to assume the risk she may need to take in allowing pregnancy to continue on the chance that she may have a living baby. If the complication of pregnancy is of such a nature that her life will be greatly jeopardized by continuation of pregnancy, she should be advised to have the pregnancy terminated because of the odds against her. This should not be a blanket decision in the case of many of the complications of pregnancy, and this applies to many cases of pre-existing vascular disease.

is less strenuous than that of men and the "hypertensives" have a better life expectancy.

There appears to be a tendency for hypertension to develop among certain families. It is probable that the married women in such families comprise a relatively high percentage of patients who have hypertensive toxemias of pregnancy and that some of their childless sisters also have essential hypertension. As mentioned previously, some patients with pre-existing hypertension, usually of the mild type, pass through pregnancy without appreciable increase in blood pressure. We have followed several of these for ten or more years without observing any more increase in the degree of vascular disease than might obtain in the nontoxemic patient.

Of interest is a group of 11 cases reported by Dieckmann. Hypertension of varying duration was present prior to pregnancy but the blood pressure either did not increase or actually fell in the course of pregnancy; four weeks or more after delivery the pressures were at the original level or in some instances higher. Adson and Allen reported a case of hypertension in which the blood pressure decreased markedly after sympathectomy, returned to the former high level when the patient became pregnant, and again decreased following therapeutic termination of pregnancy.

As the degree of vascular injury and sclerosis increases among pregnant women with severe hypertensive disease, it obviously becomes less possible for the cardiovascular renal system to maintain its function. This is especially true when the renal function is lowered appreciably. In such cases, patients commonly receive additional injury with each pregnancy so that the progress of the disease has been described as a step-ladder rise in the severity of vascular sclerosis.

In the presence of known severe chronic vascular disease or renal disease, pregnancy is contraindicated. If pregnancy occurs in such a case, particularly in a case in which there is a history of severe toxemia in a previous pregnancy or more rarely in which there is definite evidence of lowered renal function, interruption of pregnancy is advisable. Every woman is entitled to make her own decision, although the risk involved should be explained to her. Some, because of personal wishes or religious convictions, prefer to take the risk and carry on. In about 50 per cent of the cases in which the disease is severe, the patients give birth to living children. Comparatively few mothers die during pregnancy. Most of them have an increase in severity of the chronic vascular disease which probably shortens their lives. A minority go through pregnancy without apparent exacerbation of the disease.

Chronic vascular disease affects the maternal side of the placenta as it does all of the maternal tissues. Kellogg, Young, and many other obstetricians have noted the high incidence of pathologic changes in the placenta, including extensive formation of infarcts and retroplacental hematomas. The high incidence of *abruptio placentae* in cases of chronic

factors which increase the incidence of manual removal and those which increase the morbidity following the procedure (see Table I and II). The material includes those patients delivered from March 1, 1935, to March 1, 1941. During this six-year period, there were 8,902 deliveries and 74 cases of manual removal of the placenta, an incidence of 0.83 per cent. Cases in which the placenta was delivered normally and in which, because of bleeding later in the puerperium, the uterus was explored for a retained cotyledon are not included; if these cases were included, the mortality statistics would be affected more favorably on the side of manual removal.

Mortality

Three patients out of 74, or 4.05 per cent, died following manual removal of the placenta. Since there were other factors contributing to these deaths, the case histories are summarized below.

CASE 1.—R. S., a 35-year-old multipara, para iv, gravida vii, had a labor of sixty hours, which was characterized by prolonged periods of uterine inertia and premature rupture of membranes for forty-one hours. An amniotic sac infection developed and temperature rose to 103° F. Twice she received 10 gr. of quinine to improve pains. Approximately fifteen minutes after the cervix became 3½ fingers' dilated, she delivered spontaneously a stillborn, nonmacerated infant, weighing 7 pounds. Immediately she began bleeding moderately and in thirty minutes she lost 750 c.c. of blood. The uterus remained relaxed and would not contract. A manual removal of the placenta was performed under ether anesthesia after 30 minutes, and the uterus was then packed. The patient now appeared to be in shock. Vaginal bleeding continued in spite of the uterine tamponade. The total blood loss was estimated to be 1,600 c.c. While moribund she was transfused without benefit. This was before the days of the blood bank and there was unavoidable delay in securing a donor. The patient did not react and died three hours post partum.

Post-mortem examination showed a rupture of the lower uterine segment with hemorrhage into the base of the broad ligament. This was not recognized either during the manual removal or the packing of the uterus. Ten international units of pituitrin were given intramuscularly in the third stage and 0.2 mg. of ergonovine intravenously after the delivery of the placenta.

CASE 2.—M. F. was a 35-year-old multipara, para xi, gravida xv, with a twin pregnancy, confirmed by x-ray during labor. After a first stage of twenty-one hours and a second stage of two hours, a breech extraction was performed on the first infant because of failure to progress. Thirty-five minutes was then allowed to elapse; the second bag of waters was artificially ruptured and the second infant was also delivered by breech extraction. Two cubic centimeters of obstetric pituitrin were given intramuscularly twice. The operator allowed five contractions of the uterus to take place. An expression of the placenta was now attempted with the sudden loss of 700 c.c. of blood, followed by a slow but steady bleeding. After a third stage of sixty-five minutes, the incompletely separated placenta was removed manually under ether anesthesia. Much bleeding occurred during and following this procedure,

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MANUAL REMOVAL OF THE PLACENTA

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MANY authors^{1-3, 10} consider that manual removal of the placenta following pelvic delivery bears with it the greatest morbidity and mortality of all obstetric operations. The incidence of this operation is usually given as about 1 per cent of all deliveries, although some report an incidence as low as 0.3 per cent and others as high as 3.27 per cent.^{1-3, 6} Peckham, Wilson, Borborg, Currie, and others^{2, 6, 8} state that in a large general hospital where many neglected cases are admitted, the mortality is over 10 per cent. For a procedure so often considered necessary and yet so dangerous, few analyses have appeared in the American literature. If the incidence of manual removal is 1 per cent and the mortality 10 per cent, it would appear that one out of every thousand women who deliver per vaginam will die as a result of manual removal of the placenta. The authors believe that the operation is often an incidental procedure following a more serious operative delivery and consequently is accused unjustly of the resulting morbidity and mortality. Nevertheless, manual removal of the placenta cannot be considered an innocuous operation; for this reason the attendant often procrastinates in the presence of an excessive blood loss, thereby adding considerable danger to the manual removal when it is finally performed. Many lives are probably lost by this delay rather than by the operation itself.

These beliefs, as stated above, prompted a study on the obstetric service at Bellevue Hospital of the cases in which the placenta had been manually removed. An attempt was made to determine both those

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This death was chiefly attributable to post-partum hemorrhage, secondary to overdistention of the uterus by large twins and not because of a manual removal of the placenta. It is unjust to the mortality statistics of manual removal to include such deaths from hemorrhage. Yet some authors^{1, 2, 7} quoted in 6 in their eagerness not to give their own hospital too good a statistical record, include such cases and, a priori, make manual removal seem more hazardous. The third patient described above died from sepsis following a severe amniotic sac infection beginning during labor. The manual removal of the placenta was probably an important factor in the fatal outcome. Wilson⁸ has stressed the seriousness of a retained placenta in the presence of an amniotic sac infection.

The first death (that with ruptured uterus) is definitely not attributable to manual removal of the placenta. The corrected mortality can therefore be stated as 2 out of 74, or 2.7 per cent. One patient, or 1.35 per cent, died from hemorrhage, and one patient, or 1.35 per cent, from sepsis. While there shall always be an occasional maternal death from blood loss, fatal hemorrhage almost never should be directly due to the manual removal, if proper precautions are used.

Morbidity

Thirty-one, or 43.1 per cent, of 72 patients with manual removal (excluding 2 that died immediately post partum) were morbid. Very few of these patients were seriously ill. In many cases the manual removal did not appear to be the chief cause for the morbidity. In fact, there were only 21 patients who delivered spontaneously, without an amniotic sac infection, prolonged labor of over thirty hours, or a post-partum hemorrhage. Of these 21, only 5, or 23.8 per cent, were morbid. Six of the 21 were packed. Hence, only 15 patients in the series of 74 delivered spontaneously without packing or complication other than the manual removal. Of the 15 uncomplicated deliveries, 3, or 20 per cent, were morbid. The factors in our series which appear to be the most important in increasing the morbidity following manual removal are prolonged labor, intra-partum amniotic sac infections with fever, tamponade of the uterus, difficult operative deliveries, and post-partum hemorrhage. (Table I).

Duration of Labor

It is generally believed that prolonged labor increases the incidence and morbidity of manual removal and this appears true in our

TABLE I. FACTORS ASSOCIATED WITH MORBIDITY IN 74 CASES OF MANUAL REMOVAL OF PLACENTA

	NO. CASES	NO. MORBID	% MORBID
Active labor of 30 hours or more	7	5	71.4
Clinical evidence of amniotic sac infection (fever and purulent amniotic fluid)	11	7	63.6
Tamponade of uterus	21	12	57.8
Midforceps and breech extractions (excluding twins)	20	11	55
Post-partum hemorrhage of 500 c.c. or over	46	21	45.7
Deliveries without post-partum hemorrhage (includes other complications)	28	10	35.7
Spontaneous delivery (all cases)	40	14	35
Spontaneous delivery without any of above complications	15	3	20

the total blood loss amounting to 2,200 c.c. The uterus was packed with 10 yards of gauze. During this time 2 c.c. of pituitrin and also 1 c.c. of gynergen were given intramuscularly. An infusion of glucose gum-acacia solution was begun two hours after the termination of the third stage. While not in shock and seemingly in fair condition, the patient died approximately one hour after the infusion was started. At the time of death, however, blood had appeared through the packing. A transfusion had not been given due to unavoidable delay in securing a donor. No autopsy was obtained. The first infant weighed 7 pounds 2 ounces and the second infant 8 pounds 12 ounces, and both were born in good condition.

CASE 3.—S. S., a 29-year-old multipara, para iii, gravida v, was admitted to the hospital at term but not in labor, following premature rupture of the membranes thirty-five hours previously. She had an upper respiratory infection but no fever on admission. After desultory pains for two days and excellent pains for two hours she delivered spontaneously, without episiotomy or laceration, an apparently normal 6 pound 6 ounce infant. Total duration of ruptured membranes was eighty-five hours. During the last twenty-four hours of labor, the patient had an amniotic sac infection with chills and a fever rising to 103° F. The amniotic fluid was purulent and foul. Two cubic centimeters of pituitrin were given intramuscularly immediately after delivery of the infant. Uterine contractions occurred at intervals, but there was no evidence of placental separation. After forty-five minutes in the third stage, slight but steady uterine bleeding appeared. The Credé maneuver was attempted several times without success. After a third stage of one hour and a blood loss of 200 c.c., the placenta was removed manually with ease under cyclopropane anesthesia. Two-tenths milligram of ergonovine was given intravenously, and there was no further bleeding. Uterine tamponade was not performed. The total blood loss was 400 c.c. The patient continued to be febrile in the puerperium, and evidence of diffuse pulmonary emboli appeared. An anaerobic streptococcus was cultured from the blood stream. There was no response to multiple transfusions or sulfonamide therapy. She died on the 57th post-partum day. Unfortunately, no post-mortem examination was performed.

Comment

In the first case, R. S., the patient had an unrecognized rupture of the uterus. The manual removal was incidental and not a significant factor in causing the maternal death. On analyzing the second case, manual removal of the placenta was necessitated by post-partum hemorrhage during the third stage from an atonic, overdistended uterus. Also the quantity of packing utilized does not seem to have been sufficient. The circumstances of this death were peculiar since the patient was never in shock and it is possible that the death was due to the gum-glucose solution. As has been reported by Studdiford,¹¹ several deaths from gum-glucose solution occurred on the Bellevue obstetric service at this time. Nevertheless, the quantity of blood lost without replacement (2,200 c.c.) would appear sufficient to cause the death of the average patient. This was in the days before the blood bank was organized and ergonovine became available. By transfusing in the third stage and giving ergonovine liberally after the removal of the placenta, this patient might well have been saved.

35 per cent. There were 11 patients with midforceps deliveries and 9 breech extractions; of the combined 20, 11, or 55 per cent, were morbid.

It is interesting that 16 patients, 21.6 per cent of the total 74 patients, were breech deliveries, while the incidence of breech deliveries at Bellevue Hospital is only 6 per cent. Probably breech deliveries per se are not important in increasing the incidence of manual removal, but rather because they are associated with a high incidence of prematurity, or of prolonged labor and difficult delivery.

Uterine Tamponade

It appears that packing the uterus and vagina post partum increases considerably the morbidity in manual removal. Consequently, packing should be dispensed with whenever possible. In 23, or 31.1 per cent, of the patients, the manual removal was followed by tamponade of the uterus. Two died immediately after packing, and of the 21 patients, 12, or 57.1 per cent, were morbid. Fifty-one patients were not packed, and of these, 19, or 37.3 per cent, were morbid. Of the 41 nonmorbid cases in the series, only 9 were packed. There were 6 patients who delivered spontaneously without any complication other than manual removal followed by uterine tamponade; 2 of the 6, or 33.3 per cent, were morbid. There were 15 patients who delivered spontaneously without any complication other than manual removal, which was not followed by uterine tamponade; only 3 of this group, or 20 per cent, were morbid.

Post-partum Hemorrhage

Post-partum hemorrhage commonly accompanies manual removal of the placenta and frequently is the indication for this maneuver. Forty-eight, or 64.9 per cent, of the 74 cases were associated with a post-partum hemorrhage of 500 c.c. or over; 23, or 31.1 per cent, with a post-partum hemorrhage, 1,000 c.c. or over; and 8, or 10.8 per cent, with 1,500 c.c. or over. Excessive blood loss definitely increased the morbidity in manual removal, for of the 46 patients with post-partum hemorrhage of 500 c.c. or over (excluding 2 that died immediately post partum), 21, or 45.7 per cent, were morbid. Of the 21 patients with post-partum hemorrhage of 1,000 c.c. or over (excluding the 2 that died immediately post partum), 11, or 52.4 per cent, were morbid. Only 28 patients, or 37.8 per cent, had post-partum bleeding of less than 500 c.c. Ten of the 28, or 35.7 per cent, were morbid.

Of the 31 morbid cases in the entire series of 74 manual removals, 21, or slightly over two-thirds, were associated with a post-partum hemorrhage of 500 c.c. or over. Eleven, or over one-third of all the morbid patients, had a severe post-partum hemorrhage of 1,000 c.c. or over. Hence, post-partum hemorrhage increases the morbidity in patients with manual removal, the incidence of morbidity rising with the degree of hemorrhage.

Factors Which Influence Incidence of Manual Removal

The factors which appear to increase the incidence of manual removal are a previous manual removal, post-partum hemorrhage, midforceps operations and breech extraction, prematurity and immaturity of the fetus, maceration of the fetus, multiple pregnancy,

series. Of the 74 patients, 8 had an active labor of thirty hours or over. This is an incidence of approximately 11 per cent compared to the general incidence of prolonged labor of 2.5 per cent, five of 7 patients (excluding one immediate post-partum death), or 71.4 per cent, with a labor of thirty hours or over were morbid.

Amniotic Sac Infection

In this study an amniotic sac infection was said to be present if the intra-partum amniotic fluid were foul or purulent and if the temperature rose to 100° F. or over, both factors being necessary. By these standards, 11, or 14.9 per cent, of the series had an amniotic sac infection. Of these 11, 7, or 63 per cent, were morbid post partum, and none were packed. Of the 4 nonmorbid ones, one was packed but only for eight hours. Unquestionably, an amniotic sac infection increases considerably the morbidity of manual removal. It also appears to increase slightly the incidence of this maneuver. The only death from puerperal infection after a manual removal occurred in a patient with an intra-partum amniotic sac infection.

Type of Delivery

Operative deliveries, excluding low forceps, increase the incidence and the morbidity of manual removal of the placenta (Tables I, II, and III). Only 40 of the 74 patients (55.4 per cent) were spontaneous deliveries. In this group of spontaneous deliveries the morbidity is

TABLE II. FACTORS THAT APPEAR TO INCREASE THE INCIDENCE OF MANUAL REMOVAL OF THE PLACENTA

	NO. CASES	%
1. Previous manual removal of the placenta	7 of 44	15.9
2. Post-partum hemorrhage of 500 c.c. or over (includes blood loss immediately after placental delivery)	48 of 74	64.9
3. Midforceps and breech extraction operations	20 of 74	27.0
4. Prematurity and immaturity	16 of 74	21.6
5. Macerated fetus	9 of 74	12.2
6. Multiple pregnancy	4 of 74	5.4
7. Clinical amniotic sac infection with fever	11 of 74	14.9
8. Active labor of 30 hours or more	7 of 74	9.5

The above factors are arranged according to their apparent order of importance, as based on a study of 74 cases of manual removal of the placenta, the apparently more important factors being listed first.

TABLE III. TYPE OF DELIVERY WITH RESULTING MORBIDITY IN 74 CASES OF MANUAL REMOVAL OF PLACENTA

	SPONTANEOUS	LOW FORCEPS	ASSISTED BREECH	BREECH EXTRACTION WITH VERSION	BREECH EXTRACTION WITHOUT VERSION	MID-FORCEPS	TWINS
Morbid	14	0	3	3	2	6	3
Not morbid	26	2	4	3	1	5	
Died at delivery	1						1
Total	41	2	7	6	3	11	4

Twins

The presence of twins increases the incidence of manual removal chiefly because of hemorrhage caused by partial placental separation either in the third stage of labor or after the birth of the first infant. Guttmacher⁴ at the Johns Hopkins Hospital found the incidence of manual removal almost twice as high in twins as in the total clinic incidence. Four patients in our series, or 5.4 per cent, had twins. One patient died immediately post partum, and the other three were morbid. The presence of large twins is viewed with particular concern. Uncontrollable bleeding often starts after the delivery of the first infant, necessitating the prompt delivery of the second infant and then the placenta. Because of this rapid evacuation of the distended uterus even oxytocics may fail to overcome the uterine inertia. One case history in which the mother died from hemorrhage has already been given. In another case, where the infants weighed 8½ pounds each, because of continued bleeding after the manual removal, the overdistended uterus and the vagina were packed with the enormous amount of 60 yards of 2-inch gauze, which is three times the usual amount. In such cases 10 I.U. of pituitrin intramuscularly and possibly 0.2 mg. of ergonovine should be administered as soon as the second infant is delivered.

Other Factors

Thirty, or 42.9 per cent, of the 74 patients were primiparas, and 44, or 57.1 per cent, multiparas. The procedure appears especially common in multiparas who delivered spontaneously after a long labor due to uterine inertia.

There were 28.3 per cent of the series who had one abortion and an additional 14.9 per cent who had 2 or more abortions prior to the manual removal. A priori this appears to be a high incidence, but the incidence of abortions among the Bellevue obstetric patients is high. In our series, abortions, injuries due to curettage, and a history of inflammatory disease appear to play no assignable role as causative factors in retained placenta. Authors in the past have disagreed as to the importance of these factors.^{3, 6}

Sixty-five, or 87.8 per cent, of the patients subjected to manual removal were white, and 9, or 12.2 per cent, were Negroes, which is an incidence of 7 to 1. The ratio of white women to negroes on the obstetrical service at Bellevue Hospital is almost exactly 7 to 1. Hence, in our series race is unimportant. This is in sharp disagreement with the findings of Peckham² at the Johns Hopkins Hospital, where the operation was necessary much oftener in the white than in the black race.

In our series syphilis was a factor in one case of premature labor and in none of the intrauterine fetal deaths. Syphilis per se does not appear to increase the incidence of manual removal. Since, however, prematurity or a macerated infant does increase the tendency to this operation, it is conceivable that in a very large series syphilis might indirectly increase the incidence of manual removal.

Placenta Accreta

Cases of placenta accreta are occasionally reported from other institutions. For some unexplainable reason, not a single case of pla-

amniotic sac infection, and prolonged labor. Some of these factors have already been discussed, and the others are discussed below

Previous Manual Removal

It is generally agreed that a patient who has had one manual removal because of a retained placenta is more liable to have another than is the patient who has never been submitted to this operation. In a series of 189 cases of manual removal, Schie³ found that among the multiparas 64.7 per cent had a history of a previous manual removal of the placenta. In our series there are 44 multiparas, and 7, or 15.9 per cent, are known to have had a previous manual removal of the placenta. Probably this incidence should be even higher in our series since some patients who have been delivered in other hospitals might have been submitted to this procedure without our being aware of it. At any rate, it is clearly established that some patients appear to have an inherently faulty mechanism of placental separation in the third stage of labor. Either the separation is incomplete and the placenta is removed because of hemorrhage, or the placenta does not separate at all and is removed because of a prolonged third stage; the former situation occurred more commonly in our series. One patient has now been submitted to the operation 4 times. Recently a patient was delivered who already had had 2 previous manual removals; with the present delivery the placenta was finally expressed by a Credé maneuver, but only after a third stage of one hour with a total blood loss of 800 c.c.

Infant Weights

Exclusive of twins, 16 infants (21.6 per cent of 74) weighed less than 5 pounds and 8 (10.8 per cent) less than 3 pounds. Hence, the authors agree with Peekham,² who has shown that manual removal was necessary much more frequently following premature than term delivery. On the other hand, the presence of an excessively large infant does not appear to increase the incidence of manual removal. No infant in the series weighed as much as 10 pounds, and only 4, or 5.4 per cent, weighed 9 pounds or over.

Infant Deaths

In our series manual removal was associated with a high incidence of stillborn infants or very early neonatal deaths, this having occurred in 22 of 74 patients, or 29.7 per cent. Seven of these infants had a birth injury, as shown by autopsy; 6 of these followed a difficult forceps or breech delivery and only one a spontaneous delivery. Five died because of immaturity. On analysis, it appears that the deaths of the infants are merely an incidental and not a causative factor in manual removal, since this procedure is necessary much more frequently following difficult operative deliveries and following premature labor. It does appear, however, that intrauterine death of the fetus occurring many hours before delivery caused an increased incidence of manual removal. Nine (12.2 per cent of 74) patients had a macerated, stillborn infant. This group was not associated with difficult deliveries, and most of them were at term. This factor of fetal maceration appears to have been ignored in previous analyses.^{1-3, 6, 10}

of the retention or "trapping" of the placenta by the tightly contracted uterus. Consequently, the administration of ergonovine in the third stage of labor was discontinued.

The administration of adrenalin in the third stage of labor, in the hope of relaxing a possible contraction ring and thereby avoiding a manual removal, has proved a failure at the Bellevue Hospital. Thirteen patients in the series received 0.5 to 1 c.c. of adrenalin in the third stage of labor when the placenta could not be expressed. We could find no case where the use of adrenalin made manual removal unnecessary.

Following a manual removal of the placenta, it has recently been our policy not only to give 0.2 mg. of ergonovine intravenously, but also to give 0.2 mg. by mouth or intramuscularly every two hours for 6 doses. If this routine is followed it is rarely necessary to tamponade the uterus, unless it is suspected that fragments of the placenta remain. No toxic effects have been noted from the repeated dosage of ergonovine. With early transfusion and the liberal use of ergonovine, maternal deaths from hemorrhage after manual removal of the placenta should be extremely rare.

It is a moot question as to how long the accoucheur should wait before performing a manual removal. At Bellevue Hospital if the placenta has not separated after one hour, or if the patient has lost approximately 500 c.c. of blood, a manual removal is performed. This operation is seldom difficult if undertaken within an hour or two after delivery of the infant. To await an alarming hemorrhage before performing a manual removal adds an unnecessary risk to the procedure when it is finally undertaken.

In the 74 cases studied, the manual removal was done chiefly because of hemorrhage in 52 instances, because of the time element in 15, and as a prophylactic measure in 7. In at least 11 cases, however, more than one indication was present.

Summary

1. An analysis of 74 consecutive cases of manual removal of the placenta at Bellevue Hospital is given. This represents an incidence of 0.83 per cent of 8,902 deliveries over a period of six years.

2. The uncorrected mortality is 3, and the corrected mortality is 2, or 2.7 per cent, one patient dying from hemorrhage and one from sepsis. With transfusions and ergonovine, deaths from hemorrhage because of manual removal of the placenta should be extremely rare, provided the obstetrician does not await an alarming blood loss before resorting to manual intervention.

3. The uncorrected morbidity is 43.1 per cent. Manual removal of the placenta is often an incidental procedure which follows a complicated labor or a serious operative delivery and usually is accused unjustly of the ensuing morbidity and mortality. Only 21 cases of the entire series of 74 had an entirely uncomplicated labor and delivery, and 6 of these were packed after the manual removal.

4. The following factors were the most important in increasing the morbidity after manual removal; prolonged labor, intra-partum amniotic sac infection, difficult operative delivery, uterine tamponade after

centa accreta has been observed on the Bellevue obstetric service in the past ten years, during which time there were over 15,000 deliveries.

Anesthesia

Of the 74 patients with manual removal of the placenta, 38 are known to have received ether anesthesia for this operation, 13 cyclopropane, and in 22 cases the type of anesthesia was not recorded. In one instance no anesthesia was used because of strong objections by the patient. Cyclopropane appears to be the anesthetic of choice where the uterus is overdistended as in grandes multiparas, twins, and polyhydramnios. Cyclopropane induces strong, continued uterine tone, while ether favors uterine relaxation, thereby increasing the post-partum hemorrhage from the already relaxed and overdistended uterus. Where the uterus is not relaxed, or where the attendant delays terminating the third stage of labor for more than one or two hours, cyclopropane has obvious defects. In such cases an anesthetic such as ether, which favors uterine and cervical relaxation, is superior.

Special Treatment in the Third Stage of Labor

An attempt was made to estimate the blood loss during the manual removal and for a period of one hour after this procedure was completed. Unfortunately, this was not recorded on every chart, but at least 8 patients, or 10.8 per cent, had an additional blood loss of 500 c.c. or over after the manual removal was begun. Hence, it is important to realize that when one elects to perform a manual removal, the maneuver may not immediately control hemorrhage.

Anticipating the hemorrhage which may accompany or follow the manual removal, it is now routine practice in the hospital to start either a transfusion or an infusion, depending on the condition of the patient, while the patient is being redraped in preparation for the procedure. If an infusion is started the blood should be typed immediately, unless the grouping is already known. This treatment, carried out in anticipation of hemorrhage, will prevent some maternal deaths. Too often the obstetrician delays the administration of an infusion or transfusion, allowing the patient to go into hemorrhagic shock. It is then discovered that the collapsed veins can not be entered by the usual venapuncture and precious minutes are lost in exposing and entering a vessel by incision and dissection. If a macerated fetus is delivered, or the previous history or present physical findings suggest erythroblastosis, it is essential that the transfused blood be Rh negative. Plasma is an acceptable substitute if Rh negative blood is not available.^{12, 13}

For the past three years the routine medication in the third stage of labor at the Bellevue Hospital has consisted in giving an ampoule of pituitrin (10 international units) intramuscularly immediately following the delivery of the infant and 0.2 mg. of ergonovine intravenously immediately following the delivery of the placenta. Of the 74 patients in the series, 47, or 63.6 per cent, received the above medication. The remaining 27 cases, except for 3 that delivered at home, occurred before the adoption of this routine. For a short period of time intravenous ergonovine was given in the third stage of labor without other medication. While this effectively reduced post-partum bleeding, as shown by Reich,⁵ 5 of 107 patients required a manual removal because

THE TREATMENT OF VAGINITIS*

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THE treatment of vaginitis is still a common problem in gynecologic practice. The multiplicity of methods reported in the literature is prima facie evidence that no treatment thus far described has proved to be adequate.

In this report, covering a period of one and one-half years, we would like to give the results obtained in the study of 282 patients, treated by a single method, namely, the instillation of a buffered acid, water dispersible jelly into the vagina.† The acidity of this vaginal jelly was varied and also its composition by adding varying concentrations of sulfathiazole, sulfanilamide, gentian violet, or iodine. We have tried to evaluate our causes of failure or success on the basis of adequacy of treatment or the rôle of primary and secondary foci of re-infection.

The general plan of investigation followed these main lines. All patients entering the dispensary or office, presenting symptoms or abnormal findings in the vaginal secretion, were studied.

TABLE I

Total number studied	282
Private	50
Clinic (Central Free Dispensary and Presbyterian Hospital Obstetrical Clinic)	232
Race	
White	216
Negro	66
Pregnant	83
Nonpregnant	199
Age	
15-20	14
20-30	97
30-40	99
40-50	48
50-60	21
60-70	2
70-71	1

A detailed history with special emphasis on the nature of vaginal, urinary and gastrointestinal tract symptoms was taken. The vast majority of these patients presented combinations of the usual symptoms of vaginitis, such as profuse discharge, vulvar irritation, dyspareunia, leukorrhoea, or irregular bleeding. The infection in a considerable num-

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†The jelly and technical service for this investigation were supplied by the Ortho Products, Inc., Linden, N. J. We also wish to thank Miss Gertrude L. Shorter for her excellent laboratory assistance.

manual removal, and post-partum hemorrhage. Tamponade of the uterus can be avoided in most instances if the uterus is empty and ergonovine is given liberally.

5. There were 64.9 per cent of the 74 cases associated with a post-partum hemorrhage of 500 c.c. or over, and 31.1 per cent with a post-partum hemorrhage of 1,000 c.c. or over. The degree of hemorrhage was directly related to the morbidity rate.

6. The following factors were found to increase the incidence of manual removal: a previous manual removal, post-partum hemorrhage, difficult operative delivery, prematurity and immaturity of the infant, maceration of the fetus, twins, and amniotic sac infection. The importance of maceration of the fetus appears to have been disregarded in previous reviews.

7. A patient who has had one manual removal of a retained placenta is likely in a subsequent pregnancy to require a repetition of the procedure.

8. Placenta accreta has not been observed at Bellevue Hospital for the past ten years, during which time there have been over 15,000 deliveries.

9. Cyclopropane appears to be the anesthetic of choice for manual removal if the uterus is overdistended.

10. Failure to realize that hemorrhage may continue during and immediately after manual removal will cause unnecessary maternal deaths. An infusion or transfusion should be started before the manual removal in almost all cases. Rh negative blood or plasma is essential for transfusion if a macerated or erythroblastotic infant has been delivered.

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in this region varied in appearance from slight to acute infection to that of chronic cystitis cystica with hypertrophy of the anterior bladder neck glands. Acute infection was frequently associated with petechial hemorrhages about the trigone resembling acute trichomonas infection of the vagina.

TABLE II

1. Trichomonas		166
Pregnant	29	
Nonpregnant	137	
2. Trichomonas and monilia		16
Pregnant	12	
Nonpregnant	4	
3. Monilia		60
Pregnant	40	
Nonpregnant	20	
4. Nonspecific		40
Pregnant	3	
Nonpregnant	37	

Sputum and stool specimens were examined. More difficulty was encountered with the collection of bowel material at the proper time, than with any other phase of this work. We do not believe that the examination of a formed stool or stool removed with the lubricated finger will reveal the true incidence of intestinal trichomonas.

TABLE III. TRICHOMONAS INFECTION

	IN PREGNANT	IN NONPREGNANT
Total	29	137
With vaginal symptoms	22	104
With bladder symptoms	8	56
<i>Patients catheterized and urine examined:</i>		
Total	25	135
Trichomonas found	10 (40%)	28 (20%)
Streptococcus, staphylococcus, and colon bacillus	9 (36%)	52 (37.9%)
<i>Patients cystoscoped:</i>		
Total	4	66
Bladder changes	2	46

TABLE IV. TRICHOMONAS AND MONILIA

	IN PREGNANT	IN NON- PREGNANT
Total	12	4
With vaginal symptoms	12	4
With bladder symptoms	2	1
<i>Patients catheterized and urine examined:</i>		
Total	9	4
Trichomonas found	2	0
Streptococcus, staphylococcus, and colon bacillus found	3	1
<i>Patients cystoscoped:</i>		
Bladder changes	2	0

ber was an incidental finding in routine physical examination. Symptoms referable to the urinary tract, such as dysuria, frequency, urgency, nocturia, and occasionally incontinence, were almost as common as the vaginal discomfort. Many patients in whom urinary tract symptoms were present did not have microscopic, cultural, or cystoscopic evidence of infection. Patients without urinary symptoms, however, occasionally did have positive findings. These histories confirmed the usual finding that the onset or return of symptoms frequently preceded or followed the menstrual flow. A large number of recurrences, however, were immediately preceded by intestinal disturbance; in fact, many of these patients were chronic sufferers from a so-called irritable bowel, manifested by recurrent attacks of loose stools.

Physical findings varied. The vulvar skin manifestations of infection ranged from normal skin to that of widespread vulvitis, including perirectal irritation and occasionally condylomata acuminata. The vaginal mucous membrane occasionally was normal in appearance but usually revealed evidence of congestion or mucosal petechiae, often with localized evidence of infection about Skene's glands or the opening of the Bartholin ducts. Frequently cervical erosions, polyps, Nabothian cysts, or other common causes of leucorrhea were found as incidental pathology. Tender indurated sacrouterine ligaments were a rather common finding, especially in the acute stages of the infection, and probably account for much of the dyspareunia or backache.

Unlubricated speculum examination always preceded any other manipulation. In like manner, pH determinations were next made, using either a Beckman potentiometer or nitrazine paper. The glass electrode of a Beckman pH meter was inserted either directly into the vagina or if a sufficient quantity of discharge was present to fill the specimen cup (3 to 4 c.c.) the readings were made in this secretion. For all practical purposes the nitrazine paper seemed sufficiently accurate, checking with the potentiometer readings within a range of 0.5 pH.

Identification of the type of vaginitis was accomplished by microscopic examination of an unadulterated wet smear and gram stain. In questionable cases the secretion was cultured.

All urine examinations were made on catheterized specimens. Trichomonas were seldom found in the whole specimen. Not until the examination was confined to the last few drops of the residual urine (2 to 4 c.c.) were trichomonas found with any degree of regularity. The catheter was not removed until after the specimen was obtained to obviate, if possible, contamination from the urethra. Concentration of the sediment by lightly centrifuging aided in finding the Trichomonas. Determinations of pH, wet and stained smears and cultures were made of the urine. Whenever possible, cystoscopic examinations were made and repeated when indicated. Cystoscopic findings of infection usually were characterized by changes around the bladder neck. The mucosa

The patients infected with monilia alone present a somewhat different picture and are summarized in Table V.

We have included under the general heading of nonspecific vaginitis the patients in whom gonorrhea, trichomonas, and monilia were not found, but whose symptoms apparently were caused by staphylococci, streptococci, or the colon bacillus.

Table VII shows the proportional use of the primary jelly and modifications.

Measured amounts (5 c.c.) of jelly were instilled deep into the vagina at bedtime or twice daily by means of a plastic syringe. This offers a greater opportunity for the patient to treat herself adequately than previous methods we have used.

A tabulation of the urinary tract findings is given in Table VIII.

TABLE VIII

	CATH- ETERIZED	TRICHO- MONAS	NON- SPECIFIC	CYSTOSCOPIC		TOTAL
				NUMBER	BLADDER FINDINGS	
Trichomonas (nonpregnant)	135	28	52	66	46	137
Trichomonas (pregnant)	25	10	9	4	2	29
Trichomonas and monilia (nonpregnant)	4	0	1	1	1	4
Trichomonas and monilia (pregnant)	12	2	3	2	2	12
Monilia (nonpregnant)	19	0	0	0	0	20
Monilia (pregnant)	1	0	0	0	0	40
Nonspecific (nonpregnant)	10	0	0	0	0	37
Nonspecific (pregnant)	1	0	0	0	0	3
	207	40	65	73	51	282
Total number patients with trichomonas				176		
Number with trichomonas found in catheterized specimen				40		
				22.6% incidence		

A résumé of 3,323 stool examinations of about 1,100 patients by direct microscopic study and culture in the general laboratory of the Presbyterian Hospital revealed the results as shown in Table IX.

TABLE IX

	TRICHOMONAS	ENDAMOEBIA HISTOLYTICA	TRICH. AND E. HIST.
Stool examination	54	79	8
Culture	98	162	13
Both (direct stool examination and culture)	38	63	2

A summation of the results of this study of vaginitis is shown in Table X.

These examinations gave the classification of patients as shown in Table II.

Our findings associated with *Trichomonas* are summarized in Table III.

TABLE V. MONILIA INFECTION

	IN PREGNANT	IN NON- PREGNANT
Total	40	20
With vaginal symptoms	33	16
With bladder symptoms	5	1
<i>Patients catheterized and urine examined:</i>		
Total	1	2
Urine examinations were negative.		

TABLE VI. NONSPECIFIC INFECTION

	IN NON- PREGNANT	IN PREGNANT
Total	37	3
With vaginal symptoms	34	2
With bladder symptoms	9	2
<i>Patients catheterized and urine examined:</i>		
Total	10	0
Urine negative	10	0

TABLE VII

"C" (basic jelly)* pH 4.5	178
Basic jelly adjusted to pH 7.0	10
"C" containing sulfanilamide	38
"C" containing sulfathiazole	7
Sulfanilamide, sulfathiazole, and "C"	7
"C" containing gentian violet 1%	6
"C" containing iodine 1%	4
Gentian violet and "C"	7
Iodine and "C"	4
Iodine and basic jelly adjusted to pH 7.0	5
"C" and basic jelly adjusted to pH 7.0	6
Gentian violet and jelly adjusted to pH 7.0	2
Gentian violet, "C" and jelly adjusted to pH 7.0	2
Gentian violet, "C" and sulfanilamide	3
Iodine and jelly adjusted to pH 7 and "C"	1
Iodine, "C" and 3% sulfanilamide	1
Cream	1
	282
Bladder treatments	
5% argyrol, oz. 1, twice weekly	79
Sulfathiazole by mouth	4
Urotropin and sodium acid phosphate	17
*"C" orthogynol jelly with pH 4.5 (Ortho Products, Inc.)	
Vegetable gum	5%
Glycerin	10%
Boric acid	3%
Ricinoleic acid	0.75
Propyl ester parahydroxybenzoic acid	0.05
Oxyquinoline sulfate	0.025
Water to	100
pH adjusted with acetic acid to pH 4.5	

They did not return of their own accord because they no longer had symptoms of vaginitis. Relief of symptoms is not synonymous with cure. These facts indicate either incomplete cure or re-infection. From this study we are inclined to believe that re-infection is most probably from the bladder. This does not explain, however, the initial infection of the vagina which we believe follows periods of intestinal infection. The male prostate serves as a primary focus in some instances. This leaves other unknown sources yet to be determined. Due to the prevalence of urinary tract contamination a similar invasion of the upper Müllerian tract probably does occur more frequently than has been indicated in the literature. Our experience in private practice with acute or chronic pelvic infection has been that they are more often associated with trichomonas or non-specific organisms, than they are with gonorrhea. These pelvic infections may be due to the bacteria associated with the trichomonas as we never have been able to isolate the trichomonas from aspirated material. The fluid from two Bartholin cysts contained trichomonas and in our opinion is a frequent cause of acute Bartholinitis. A study of secretions obtained from above the external os might offer important information concerning re-infection. By the same inference, more careful study of upper urinary tract pathology will probably accord to these infections affecting the trigone a more important rôle than at present. We are impressed by the fact that those patients in whom bladder changes were found generally had a more patulous urethra than normal. The urinary meatus in some of them was almost funnel shaped. Urethral diseases, such as granulations or partial stricture, were occasionally found.

Conclusions

1. A buffered acid jelly is an effective and acceptable method for the treatment of vaginitis.
2. A shift in vaginal pH can probably be produced by a buffered acid jelly.
3. Symptomatic relief can be obtained in a high percentage (84 per cent of patients) by this method.
4. A large number of apparent cures of monilia and nonspecific infection are reported.
5. The percentage of cures obtained compared favorably with methods we previously have employed.
6. Final cure has not been as frequent in our hands by any method as has been reported in many clinics.
7. Treatment of concomitant urinary tract infection has helped to increase our number of good results. We feel that this has been a rather neglected aspect of the treatment of vaginitis.
8. Cooperative effort between the genitourinary and gynecologic specialties would benefit the patient.

TABLE X

	TOTAL NO. STUDIED 282	CURED		RE- LIEVED SYMP- TOMS	INSUFF. TREAT.*	NOT CURED	CURED OF TOTAL CASES STUDIED	COR- RECTED % OF CASES†
		VAG.	BLAD.					
Trichomonas	Preg. 29	11	3	26	5	13	37.9	45.8
	Nonpreg. 137	53	16	107	42	42	38.6	55.7
Trichomonas and monilia	Preg. 12	1	1	10	9	2	8.3	33.3
	Nonpreg. 4	3		4	0	1	75.0	75.0
Monilia	Preg. 40	26		38	12	3	65.0	92.8
	Nonpreg. 20	14		17	3	2	70.0	82.3
Nonspecific	Preg. 3	3		3	0	0	100.0	100.0
	Nonpreg. 37	24		34	10	3	64.8	88.8

*Contains those patients who abandoned treatment and could not be followed. Their ultimate condition at time of discontinuance is unknown. Some of the latter had experienced relief of symptoms before discontinuing visits.

†The corrected percentage of cures eliminates those who had insufficient treatment according to our standards.

Discussion

We believe that the instillation of a vaginal jelly is the most satisfactory method of self-treatment for the patient, and produces results equally as good as any method we thus far have used in the treatment of trichomonas.

Additions of various chemicals have not appreciably increased the ultimate cures. Increased irritation was caused not infrequently by the addition of 1 per cent gentian violet. The addition of sulfanilamide or sulfathiazole in amounts varying from 3 to 30 per cent was no more efficacious than the basic jelly, except that the smears seemed to show a more rapid disappearance of cocci. Absorption into the blood stream of these sulfonamides could not be demonstrated, although as much as one ounce was instilled daily for a period of five days.

The paradoxical cure of the monilia vaginitis by an acid jelly in such a high percentage of cases is hard to explain. It was more effective for monilia than for trichomonas in this series. We plan to investigate further the rôle of the separate components of the basic jelly. The jelly offers, we believe, a safe method of treating vaginitis during pregnancy as no untoward results were noted in our patients.

In general, the shift of pH was toward normal vaginal acidity. Our observations confirm those of other investigators, that the pH of the vagina varies in its different portions as well as in the different phases of the menstrual cycle or amount of cervical secretion. We are not convinced that changing the pH of the vaginal secretion is the prime factor in freeing the vagina of infection, though symptoms are usually relieved. In support of these statements, 115 were considered cured as gauged by our standards while 239 of the total were symptom free. The standard for cure chosen was three consecutive negative smears obtained at the end of at least a three-month period of treatment. This criterion of cure, however, is only arbitrary, since a recent follow-up revealed that the vaginas of many of the patients still harbored infection.

DR. ALLEN (closing).—If we study these cases over a long period of time, we will find a great many of them recur. Whether that is due to lack of primary cure or re-infection is still to be determined. We are impressed also with the number of cases of pelvic abscess and salpingitis that are probably due to trichomoniasis or associated infection with yeast.

I think a great many of our postoperative infections and morbidities are due to an unrecognized vaginitis. Many times radical operations are done on the cervix, because one slide is taken and nothing found. Every one of us must realize that in a patient with acute infection with the trichomonas it may take some time to find the organisms.

As we study these cases we will find that some of the infections probably come from the gastrointestinal and urinary tracts. We should cooperate with the gastroenterologists and find out whether this infection comes primarily from the bowel.

THE IMPORTANCE OF THE RH BLOOD FACTOR IN ERYTHROBLASTOSIS*

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THE Rh blood factor recently demonstrated by Landsteiner, Wiener, and Levine and his associates is of great clinical importance, because of its possible relation to severe or fatal transfusion reactions and to the etiology of erythroblastosis. Several recent publications¹⁻⁷ have described this factor and the relation it seems to bear to these two conditions, so that it is unnecessary to review the material in detail. Suffice it to say that the Rh factor is an antigenic substance found in human blood cells which is similar in some ways to other previously described antigenic factors, the most important of which are A, B, M and N. It is inherited as a Mendelian dominant as are the others. It occurs only in the red blood cells as do M and N, and is not found in tissues and secretions as are A and B. No spontaneously occurring agglutinins for the Rh factor have been demonstrated and in this respect it resembles M and N; such agglutinins are present for A and B. When cells containing the Rh factor (Rh+) are introduced into the blood stream of a person in whom the factor is absent (Rh-), agglutinins against it may be developed (i.e., it has iso-immunizing ability). Agglutinins are never produced for the M or N factor. For this reason the M and N factors are of no importance in blood transfusions while the Rh factor is of much importance. If blood containing the Rh factor is introduced into an individual who is Rh negative, and antibodies are produced which are capable of agglutinating Rh

*Read at a meeting of the Chicago Gynecological Society, April 17, 1942.

9. Greater interest on the part of the gastroenterologist would undoubtedly give added information.

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Discussion

DR. H. C. HESSELTINE.—Much of what Dr. Allen and Dr. Baum have presented agrees sufficiently with some of our views that we cannot offer very divergent opinions.

The fact that they presented their data without correction may explain why 16 per cent of their vaginal trichomoniasis patients did not obtain relief by a single method of treatment. A careful survey of the literature or a critical study with a sufficient number of patients would bring one most likely to a somewhat similar conclusion. The results may be made to vary from a very favorable report to an average one depending upon the criteria for cure. The more rigid the criteria, the less favorable the result. As the essayists have pointed out, the patients should be followed for some time after apparent cure if one is to be certain of the results. It is especially important to examine the patients immediately after the completion of the catamenia.

Whenever one plans a new therapy it may be well to investigate the great number of medicaments and procedures which have received at least temporarily some support and perhaps popularity. From violent scrubbing of the vagina to the simple topical application, from frequent to infrequent office visits, from liquids to powders the pendulum has swung and returned.

Allen, Jensen and Wood, in 1935, pointed out the importance of the patient's own urinary tract as a focal site. We agree that too little attention is paid to such sites as the patient's urethra and bladder, cervix and gastrointestinal tract, and even to her husband. Instances occur in which both the prostatic secretion and the patient's own urinary tract may be focal sites. Bowers and I have data which confirm some of these previous reports and emphasize even more the significance of these sites as sources of recurrence. Obviously then therapy must be directed at the vaginal condition and at all other involved areas. Fortunately most of the mild or early cases yield to many and various treatments.

Drastic or extreme procedures upon the cervix and other structures will be indicated rarely and only after due consideration. The old question of the importance of the Trichomonad and the associated bacterial flora persists. Recently Wolter, Campbell, and I observed that experimental production of vaginal trichomoniasis in human beings was much more likely when there was an abnormal bacterial flora present.

If it is the increased acidity that is beneficial then any sufficiently acidie substance would produce the same response. Perhaps the value may rest with other substances in the jelly, as fragaeanth, glycerin, or the preservative in it.

Many members of this Society have their favorite therapies. It is recommended that enthusiasm be tempered with balance and control, and without correction of data. Let us all follow the example of Allen and Baum in making a thorough and complete study, just as they are in the process of doing. Likewise, let us not be premature in arriving at conclusions. Let us know what our preparations are and evaluate each substance in them. And let us not forget the likelihood of re-infection from the difficult cases.

of the interest of a physician in the Rh of the blood, forms the basis for the figures which follow.

All of the determinations have been made in the laboratories of the Mt. Sinai Hospital. Serum for testing was obtained from 5 patients with agglutinins in the blood, and all specimens on which Rh determinations have been made were tested with at least three sera. Immunization of rabbits with rhesus monkey blood has also been accomplished and this serum has been used in some cases in addition to the other three sera.

The tests have been performed according to the method suggested by Levine. Two drops of the serum containing anti-Rh agglutinins were placed in a test tube of 7 mm. bore, and to this was added one drop of a 1 per cent suspension (in saline) of the cells to be tested. The tube was shaken and placed for one hour in a water bath at 37° C. If clumping was absent at the end of that time the tube was centrifuged for one minute at six hundred revolutions. If, after the tube was shaken, the cells still failed to show visible agglutination, one drop was examined under the microscope. Known Rh+ and Rh- blood cells were always run as a control simultaneously with each test. In the early phases of the work a similar test was set up at icebox temperature. This was later discontinued in view of our own experience and that of Levine which indicates that the Rh reaction is as a rule characteristic of that exhibited by so-called warm agglutinins.

Discussion

The conclusions which must be reached as a result of this multiple testing are (1) that the Rh factor is not a single constant entity, but is rather a mosaic of factors each of which may show some individual variation and (2) the agglutinins in the rabbit serum are not identical with those produced in human blood. Although blood from the majority of all individuals reacts uniformly with the various testing sera, there are occasional instances in which blood may be negative to one serum and positive to another. If the blood of any individual is not agglutinated by a serum known to contain anti-Rh agglutinins which are effective on other bloods, it means that the particular individual whose blood fails to react is capable of becoming immunized by any blood which is agglutinated by the testing serum. If, for instance, a wife is Rh+ to two sera and Rh- to a third, while the husband is Rh+ to all three, it is evident that an Rh fraction is present in his blood to which she may become immunized. An antigenic analysis of the Rh factor has been published recently by one of us (I. D.).⁸

The blood of 60 mothers giving birth to babies with erythroblastosis has been examined. The infants of 55 mothers have died and have been examined at necropsy;* those of five mothers are living. Of these mothers 54 are Rh-, and 6 are Rh+. Among the 6 who are Rh+, 3 babies were macerated and 3 were not. In a badly macerated fetus the diagnosis is

*Sixty-six infants of these mothers have been examined at autopsy at the Chicago Lying-In Hospital, and five, delivered in subsequent pregnancies, have been examined elsewhere. One mother gave birth to twins both of whom died of the disease. Thirteen mothers have had a single subsequent pregnancy and one had two subsequent pregnancies. All infants have died of erythroblastosis.

positive cells, the introduction of Rh positive blood by subsequent transfusion into such a sensitized person may result in the agglutination of the donor's cells in the recipient's blood stream even though both individuals are of identical major blood groups (AB, A, B, O).

If a fetus inherits the Rh factor from an Rh+ father, and the mother is Rh-, a break in the placental circulation will result in the introduction of fetal Rh positive cells into the maternal Rh negative blood. Levine and others postulate that iso-immunization may thus be produced and that the antibodies thus formed may be transmitted back through the placenta from the maternal circulation into the fetal blood stream. These antibodies may adversely affect the hematopoietic system of the fetus and produce the condition known as erythroblastosis.

Levine and his associates have tested the blood of over 1,000 individuals and have found that, in the general population, 86 per cent of all individuals are Rh positive; 14 per cent are Rh negative. They have also shown that in a group of 111 women who have given birth to babies with erythroblastosis only 9 per cent are Rh positive while 91 per cent are Rh negative. Javert has also tested 14 mothers stated to have had babies with erythroblastosis; 11 were Rh positive, and 3 were Rh negative.

The diagnosis of erythroblastosis can be established at autopsy in the majority of cases without much difficulty. There are times however when pathologic changes are slight or are atypical and it is impossible to be certain whether or not this condition exists. Among infants who survive, even greater difficulty may be encountered in positively establishing the diagnosis. Because of the bad prognosis for future pregnancies after the condition has once occurred, the diagnosis is of more than academic interest and it is extremely important to arrive at an accurate conclusion.

We have hoped that the determination of the presence or absence of the Rh factor in the maternal blood stream might prove of diagnostic aid in the questionable cases.

As previously stated, Levine has shown the Rh factor to be absent in only 14 per cent of the general population but absent in 91 per cent of women giving birth to babies with erythroblastosis. He does not state, however, what criteria were used to establish the diagnosis of erythroblastosis in the infants of the mothers who were tested.

Material

During the past several years many fetuses and infants have been examined at autopsy, at the Chicago Lying-in Hospital. These have come both from the service of this hospital and from other institutions and individual physicians. Following the discovery of the Rh blood factor, an attempt was made to obtain blood from all of the women who had given birth to infants and fetuses in whom there had been at any time a suspicion that erythroblastosis was the cause of death. This material, together with a few additional cases submitted because

or two sera. Of those with later deaths 27 were positive to all sera, 4 were negative to all sera, 5 were negative to one or two sera.

The blood of 29 husbands has been examined; all but 2 were Rh+. One of those who was Rh- was the father of a baby with erythroblastosis.

The blood of 59 infants and fetuses has been tested. Only 6 were Rh-. In three of these the mother was Rh+; in three Rh-. In one of the latter cases where the mother and infant were both negative the diagnosis was erythroblastosis and the mother exhibited anti-Rh agglutinins. (Nine of the mothers of this group of infants were not tested.)

Among all of the mothers in our series who had babies with definite evidence of erythroblastosis 90.0 per cent are Rh negative; among all of those with abortions or deaths from other causes, only 25 per cent are Rh negative. This would seem to indicate that the Rh factor is of little importance in association with fetal deaths due to causes other than erythroblastosis. It also suggests that if the diagnosis is at all doubtful, the presence of the Rh factor in maternal blood is supportive evidence against the diagnosis of erythroblastosis.

Anti-Rh agglutinins have been demonstrated in only 10 women who have had infants with erythroblastosis. They have been present as late as two years following pregnancy.* Anti-Rh agglutinins have also been found in two women during pregnancy who subsequently gave birth to normal babies and who had never previously had infants with erythroblastosis.

Two women among the entire series giving birth to fetuses or infants which have been examined at autopsy and in which the diagnosis of erythroblastosis was established are now dead. One of these mothers had given birth to four normal children followed by five successive fetuses with erythroblastosis, all of whom we examined at autopsy. The other had had one normal child followed by five unsuccessful pregnancies, the last being the only fetus we were privileged to examine. Each mother died shortly after a transfusion (her first in each case) which was followed by a very severe reaction associated with oliguria and evidence of uremia. It is probable that both reactions were due to incompatibility of blood caused by the presence of anti-Rh agglutinins. Both women died prior to the discovery of the Rh factor.

Summary

Although 86 per cent of the population is Rh positive, isoagglutinins are not ordinarily present in the 14 per cent who are Rh negative (in contrast to the A and B antigens on which the main blood groups are based); in an individual who is Rh- (who does not naturally have the Rh antigen), agglutinins can be produced by the introduction of the Rh antigen into the blood stream.

This introduction can be accomplished either by transfusion or by transfer, during pregnancy, of the Rh antigen from the fetal to the maternal circulation.

When the mother is Rh- and the father is Rh+, either 50 or 100 per cent of the offspring will be Rh positive, the difference in percentage being dependent on whether the Rh factor in father is homo- or heterozygous. If fetal blood containing the Rh factor crosses the placental barrier and gains access to the maternal circulation, agglutinins may be produced in her blood.

*Subsequently one patient was found to have agglutinins six years after the last pregnancy.

TABLE I. THE RH FACTOR IN MATERNAL BLOOD IN RELATION TO THE AUTOPSY DIAGNOSES ON THE FETUSES AND INFANTS OF UNSUCCESSFUL PREGNANCIES

MATERNAL BLOOD	RH++		RH---		RH+- OR +--		TOTAL	AGGLUTININS PRESENT
	NO.	%	NO.	%	NO.	%		
Erythroblastosis	6	10.0	54	90.0	0		60	10
Not erythroblastosis:								
Suspected clinically	23	72.0	4	15.5	4	12.5	31	
No evidence clinically	27	75.0	4	11.0	5	14.0	36	1
Abortions	34	75.5	5	11.2	6	13.3	45	
Total mothers	90		67		15		172	11

sometimes difficult to establish, but in reviewing the case histories, autopsy protocols, and histologic sections of these fetuses, the diagnosis still seems warranted in spite of the presence of the Rh factor in maternal blood.

In all of the infants examined at autopsy the liver and spleen were enlarged, ectopic foci of erythropoiesis were present, and there was an increase in nucleated red cells in the peripheral blood. A description of the pathologic lesions found in these infants will be published by one of us (E. P.) in the near future.

Among 31 mothers giving birth to infants and fetuses on whom someone for some reason had made a diagnosis of erythroblastosis, but in which the diagnosis was not substantiated at autopsy, 5 were negative to all sera, 4 to at least one serum, 23 were positive to all. Thirteen of these diagnoses were based on fetal hydrops (10 Rh+, 3 Rh-) while the others were based on jaundice, increased numbers of circulating normoblasts, or other disturbances (14 Rh+, 4 Rh-).*

Two additional mothers who were suffering from active syphilis gave birth to babies (of one of these women two infants were examined) each of whom showed evidence of typical erythroblastosis plus syphilis. One mother was Rh+, the other Rh-. It has not been definitely established whether syphilis in itself may produce a condition identical to erythroblastosis or whether the two diseases are coincidental. We are inclined toward the latter view.

In order to determine what relation fetal and neonatal deaths not due to erythroblastosis may have to the Rh factor in the mother, the blood of 45 women whose pregnancies ended in abortions, and 36 whose infants were stillborn or died shortly after birth from causes other than erythroblastosis were examined. Of those with abortions 34 were positive to all sera, 5 were negative to all sera, 6 were negative to one

TABLE II. THE RH FACTOR IN INFANT'S AND HUSBAND'S BLOOD IN RELATION TO THAT IN THE MOTHER'S BLOOD

MOTHER'S BLOOD	RH+		RH-	
	+	-	+	-
Infant's Blood:				
Erythroblastosis			25	2
Not erythroblastosis	14	2	1	4
Husband's Blood:				
Erythroblastosis			21	1
Not erythroblastosis	4	1	2	

*There have been eleven subsequent pregnancies in this group; all have resulted in the birth of normal children.

may create a situation in which the occurrence of erythroblastosis becomes a possibility, there must be other superimposed factors which determine whether or not the possibility will be realized.

A few women giving birth to babies who appear to suffer from erythroblastosis are Rh positive and a few infants suffering from the disease are Rh negative. It may be possible that these infants are actually suffering from a different disease entity. It is certain that severe jaundice or generalized edema can occur independently of erythroblastosis, and it is possible that in a small proportion of those infants who have the fundamental disturbance in the formation and destruction of erythrocytes which is usually characteristic of erythroblastosis, the condition may be a response to an entirely different etiologic agent. Only further investigations can settle this point.

It seems justifiable, however, to conclude that in any case where the diagnosis of erythroblastosis is doubtful, support for the diagnosis is obtained by finding the maternal blood Rh negative and the paternal and infant blood Rh positive. If the mother is Rh positive, the diagnosis of erythroblastosis is less probable.

Conclusions

The introduction of the Rh antigen into an individual in whom it is not normally present may result in the production of anti-Rh agglutinins.

The introduction of the antigen may be accomplished by transfusion with Rh+ blood or by passage through the placental barrier of Rh+ cells from the fetal circulation.

If anti-Rh agglutinins are produced, the subsequent introduction of large amounts of blood containing the Rh antigen may result in a fatal reaction.

If anti-Rh agglutinins are produced, a subsequent pregnancy may terminate unfavorably because agglutinins transferred to the fetus may cause erythroblastosis.

In suspected cases of erythroblastosis the absence of the Rh-antigen in the maternal blood, associated with its presence in the paternal blood, lends support to the diagnosis.

We wish to express our gratitude to the many physicians and hospitals who have aided in the follow-up of the patients giving birth to these babies with erythroblastosis, and to Dr. Philip Levine for supplying the serum with which the study was commenced.

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If agglutinins are produced either as a result of direct intentional transfusion or by occult transfusion from the fetus, the subsequent introduction of large amounts of blood containing the Rh antigen will result in the agglutination of this newly introduced blood and a fatal transfusion reaction may occur.

When it becomes necessary to transfuse an infant suffering from erythroblastosis, the mother's blood should never be used. If, as we believe, the disease is due to the effect on the fetus of agglutinins transmitted to it from the maternal circulation, further introduction of maternal blood would result in the introduction of more agglutinins which would aggravate the disease.

It has been contended that Rh negative blood should always be used to transfuse these infants because, in spite of the fact that they are practically always Rh positive, there is a possibility of free anti Rh agglutinins being present in their blood stream. We have not observed such agglutinins and have been unable to find a record of their demonstration. It may be questioned, therefore, whether it is necessary to transfuse with Rh negative blood on this basis.

If cells and serum of patient and potential donor show no agglutination after incubation at 37° C. for one hour followed by centrifugation at 600 revolutions for one minute, the blood of this donor can be used with safety, regardless of whether it is Rh positive or Rh negative.

Since the majority of women who give birth to babies with erythroblastosis are known to be Rh negative and may show anti-Rh agglutinins, it is essential to use blood from a known Rh negative donor if it becomes necessary to transfuse one of these women.

Since the Rh factor is present in approximately 86 per cent of the general population, about 12 per cent of all marriages will be between couples where the wife is Rh negative, and the husband Rh positive. It is in this group that the wife is capable of becoming sensitized to the Rh factor and of subsequently reacting on the fetus to produce erythroblastosis. Erythroblastosis, however, occurs in only a small percentage of these women and in our experience has been found in only about 0.1 per cent of all pregnancies (The Chicago Lying-in Hospital). To account for the difference between potential and actual incidence, there are several conditions which may contribute: (1) in childless or one-child marriages the limitation in the number of offspring makes the production of erythroblastosis impossible, (2) the Rh antigen in the infant may vary in its ability to stimulate the production of agglutinins in the maternal blood, (3) the ability of the placenta to prevent the passage of the Rh antigen may vary, (4) the maternal response to the introduction of the Rh antigen into the blood stream may vary, (5) the ability of the placenta to permit passage of agglutinins may vary.

It becomes apparent that although a fundamental incompatibility between the genetic constitution of the male and female germ cells

SARCOMA OF THE UTERUS

A Clinicopathologic Study of Twenty-Seven Cases

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THAT the evaluation of criteria of malignancy in uterine connective tissue tumors has been attended by considerable uncertainty is indicated by the many published attempts to establish reliable criteria. While several authors^{1, 2} have stressed the number of mitotic figures as important, others³ have stated that nothing short of metastasis is reliable for diagnosis. There is further evidence of this confusion in the wide variations in published reports of the ratio of sarcoma to fibroids of the uterus. These have ranged from less than 1 per cent to more than 10 per cent.

This uncertainty in diagnosing sarcoma of the uterus has been experienced in this laboratory also. It was felt that a follow-up of the cases was necessary to evaluate criteria for this diagnosis. For this reason a study of cases diagnosed sarcoma of the uterus in this institution was undertaken.

There were 27 of these since 1928 and in all of them the postoperative course has been followed. Only three surviving patients, because they were recent cases, were followed less than five years. The essential data of the cases have been summarized in tabular form (Table I).

Discussion

The most striking feature of this series is that invasiveness, gross or microscopic, closely correlates with a subsequent malignant clinical course. Of 13 patients whose specimens showed gross or microscopic evidence of invasiveness, all died or had recurrence. Proof of malignancy was established in 10 of these, but in the other three the degree of malignancy of the tumor appears indefinite (Cases 7, 13, and 23).

Of the 14 patients in whom the tumor showed no gross or microscopic evidence of invasion, 12 are living and well, mostly five or more years after operation. One patient died of pneumonia and the exact cause of death is not known in the other case, although it appeared not to be sarcoma.

Thus, the benign clinical course of the cases in which evidence of invasiveness was absent; and the fatal outcome of nearly all patients in which such evidence was present would make it appear that gross or microscopic evidence of invasiveness is a fairly accurate criterion of malignancy.

Discussion

DR. RAPHAEL ISAACS.—The work on the Rh factor has shown that the classifications of certain causes of neonatal deaths are now out of date. The three common conditions in newborn infants in which a great number of nucleated red blood cells appear have been grouped together and it has been stated that these are all manifestations of the same process. We can now separate erythroblastosis fetalis as it is quite different from the other members of the group.

What are the mechanisms by which the changes of erythroblastosis are produced? There are probably several. First, the blood of the baby dissolves more quickly than normal, for we see products of destruction in the bile cells and at the same time stabilization of the products of hemoglobin degeneration, indicating that hemolysis takes place in the fetus much more rapidly than normal. As a result the fetus tries to produce the red cells faster to compensate for this great loss. Another factor is the lack of oxygen, for the fetus evidently has great difficulty in getting oxygen from the mother. For this reason also the baby tries to make red blood cells faster than normal and they are poured out as immature forms. When the baby is born it still shows this lack of oxygen for it is dyspneic and cyanotic and its heart is much larger than normal. Evidently the heart has been working very hard to try to do with blood low in oxygen what it usually does with normal blood.

A few years ago we knew nothing about the Rh factor. I wonder if there are not others factors which we do not know. Perhaps there is another condition very much like this one in which the mother is Rh positive and the infant Rh negative. Of course under such circumstances one would not expect erythroblastosis.

DR. EDWARD L. CORNELL.—I would like to ask Dr. Potter what tendency there is for fetal hydrops to occur in different pregnancies. Many years ago I had a patient who had her first pregnancy with fetal hydrops and marked hydramnios, then five normal babies, and then the next pregnancy was a duplicate of the first. This was some fifteen years ago, when we knew nothing about the subject being presented tonight. In this case the husband and wife were first cousins.

DR. FRED L. ADAIR.—We have had a number of these cases and I have found evidence of syphilis in a rather high percentage. I wonder if in the patients who had erythroblastosis whether syphilis was present.

DR. ISRAEL DAVIDSOHN.—I have wondered what was the reason for the rapid acceptance of the Rh factor and the theory of the cause of erythroblastosis. One reason was that the discovery of the Rh factor was made by Landsteiner, the greatest living authority on blood groups. Then there has been a great deal of interest in the associated transfusion reactions to which Dr. Potter referred. Finally the ground for the hypothesis of erythroblastosis had been well prepared, for several years ago Darrow offered isoimmunization as a possible explanation for erythroblastosis.

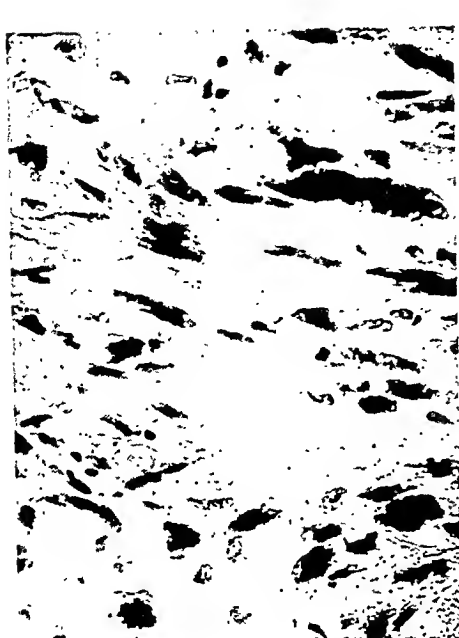
I believe we are justified at the present time in concluding that there are at least three different factors in Rh positive individuals. Some people have all three, some have two, and some have only one. What is the practical significance of that conclusion? That it is necessary, as Dr. Potter mentioned, not to be satisfied with the use of only one typing of serum against the Rh factor, but to use at least three. Possibly later we will find that there are more than three.

Another important factor is that some of these serums agglutinate monkey's blood but not human blood. That means that there are differences between the Rh factor in man and the Rh factor in the monkey. I am emphasizing this, because in the enthusiasm that follows the interest in this work there may be a tendency for it to be tried out by people who do not have enough experience to evaluate the many inherent sources of error.

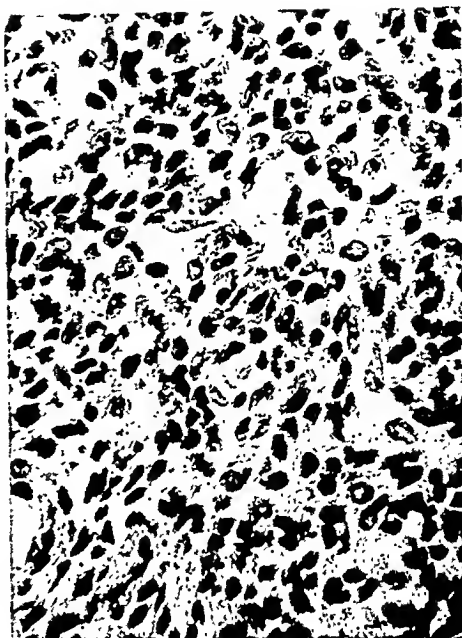
TABLE I. SHOWING CLINICAL AND PATHOLOGIC FEATURES

CASE	COLOR	AGE AT OPERATION	PARTY	AGE AT MENOPAUSE	ABNORMAL BLEEDING	PAIN	ABDOMINAL TUMOR	SUPRAVAGINAL HYSTERECTOMY	PAN-HYSTERECTOMY	DEEP X-RAY	ARISING IN FIBROID	ENCAPSULATED	INVADING
1	W	51	0	49	-	+	+	+	-	+	+	-	+
2	W	37	iv	--	+	+	+	+	-	-	+	+	-
3	W	49		46	-	+	+	+	-	-	+	+	-
4	W	51	0	50	+	-	+	+	-	+	+	+	-
5	W	46	0	44	+	+		-	+	+	-	-	+
6	W	66	ii	45	+	+		-	+	+	+	-	+
7	W	55	i	49	+	+		-	+	-	-	-	+
8	W	57		55	-	+	+	+	-	+	-	-	+
9	W	44	vi	--	+	+	+	+	-	-	+	+	-
10	W	56	i	50	-	+	+	+	-	-	-	-	+
11	W	64	viii	45	+	-		-	-	+	-	-	+
12	W	37	ii	--	+	-	+	+	-	-	+	+	-
13	W	66	ii	55	+	-		-	+	+	-	-	+
14	W	57	iii	55	+	+	-	2½ yr. ago	-	-	-	-	+
15	W	37	0	--	+	-		+	-	+	+	+	-
16	B	38	0	--	-	+	+	+	-	-	+	+	-
17	B	42	xiii	--	+	+	+	-	+	-	-	+	-
18	W	47		--	-	-	+	+	-	-	+	+	-
19	W	38		--	+	+		+	-	-	+	+	-
20	W	68		50	+	+	-	4 yr. ago	-	+	-	-	+
21	W	66	vi	52	+	-	-	-	+	+	-	-	-
22	W	65	vi	50	+	-	-	-	+	+	-	-	-
23	W	55	ii					-	+	-	+	-	+
24	W	59		53	+	-	-	-	+	+	+	+	+
25	W	30		--	+	+		+	-	+	+	-	-
26	W	49	0	--	-	+	+	+	-	+	+	-	-
27	W	58	ii	48	-	+	-	+	-	+	-	+	-

*-, absent or rare. +, mild to moderate. ++, moderate to marked. +++, very marked. (The



A.

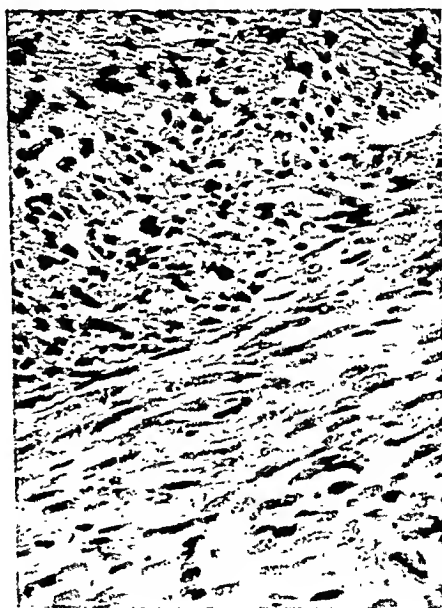


B.

Fig. 1.—Photomicrographs from Cases 16 (A) and 25 (B) showing malignant microscopic appearance. The clinical course of both has been benign. Note large mitotic figure at bottom of 16 and marked cellularity of 25.



A.



B.

Fig. 2.—Photomicrographs from Cases 8 (A) and 14 (B) showing a less malignant microscopic appearance. Both cases died with metastases. Cell morphology rather uniform in both and mitotic figures not found. Note arrangement in bundles in Case 14.

On the other hand, the various microscopic features such as increase in cellularity, variability in cellular morphology, anaplasia, giant cells, hyperchromatic nuclei, and even mitoses have not been reliable criteria of malignancy in this series of cases. While there is some correlation, a number of notable exceptions are found. Cases 2, 3, 12, 16, 17, 22, and 25 are examples in which the tumors appeared definitely malignant (Fig. 1) as judged by these criteria, and yet all the patients are well a number of years after operation. Cases 8, 11, and 14 are examples in which the tumors appeared less malignant (Fig. 2) as judged by the same criteria and yet metastasized to distant areas and caused death of the patients.

Most fatalities occurred within three years after the diagnosis was established. So far as this series is concerned, patients that survived even two years seem to have an excellent chance of cure. An exception to this is the patient in Case 24, who has had a recurrence for at least the past year but is still alive three and one-half years after operation.*

The ratio of the diagnosis of sarcoma uteri to fibroid uteri in this laboratory since 1928 has been approximately 2 per cent. While reports in the literature have given an incidence ranging from below 1 per cent to over 10 per cent, the average given has been 2 to 4 per cent. Obviously the higher figures probably consider "cellular fibroids" as sarcomas. Even with the relatively low incidence of sarcoma uteri in the present series, over 25 per cent of the patients survived five to twelve years following routine treatment as though they had had only ordinary fibroids.

Sixteen of the 27 tumors apparently arose in fibroids. Ten of the 16 patients are known to be well, mostly five or more years after operation. Two died of causes other than sarcoma. Three have died of sarcoma and the sixteenth has a recurrence. Thus the proved malignancy in this group is only 25 per cent. Only two of the 11 patients whose sarcomas apparently did not arise in fibroids are well. It is not certain if sarcoma was the cause of death in 3 of this group, but 6 of the 11 tumors, or nearly 55 per cent, have been proved malignant.

Corscaden and Stout⁵ found that the autopsy incidence of sarcoma in myomatous uteri was extremely low. They also found only 4 cases of proved sarcoma of the uterus following radiation therapy alone in over 40 thousand cases of fibromyoma.

From this study it would seem advisable to use caution in making the diagnosis of sarcoma of the uterus, particularly in those arising in fibroids. Unless there is definite gross or microscopic evidence of invasion it appears likely that a fairly good prognosis should be given regardless of other microscopic features. The attention of the surgeon should be called to the presence of unusually cellular or otherwise "suspicious" tumors but unless evidence of invasiveness is noted it might be well not to call them sarcoma, which usually connotes a bad prognosis.

*This patient has died since of sarcomatous metastases, three years and nine months after operation.

CELLULARITY	VARIABILITY IN CELL MORPHOLOGY	ANAPLASIA	GIANT CELLS	HYPER- CHROMATIC NUCLEI	MITOSES	POST- OPERATIVE RESULT	REMARKS
+++	+++	++	+++	+++	++	Died (Date ?)	Extension in pelvis at operation. Hard mass in cul-de-sac one month postoperative
+++	++	+	+	+++	+	Well 12 yr.	
++	++	+	+	++	+	Well 12 yr.	
+++	++	+	++	+	+	Died 1 yr.	Pneumonia cause of death
+++	++	++	+	++	++	Died 1 yr.	Metastases in lymph nodes at operation. Origin in endometrium?
+++	++	+++	+	+++	+++	Died 2 yr.	Well differentiated adenocarcinoma of uterus mixed with sarcoma. Sarcoma cause of death
++	++	++	+	++	++	Died (Date ?)	Areas of partially differentiated adeno- carcinoma mixed with sarcoma. Cause of death sarcoma?
++	+	+	-	++	-	Died 3 mo.	Mesenteric metastases of sarcoma at autopsy. Papillary cystadenocarcinoma of ovary incidental finding
+++	+	+	-	+	-	Well 7 yr.	
+++	++	++	+	++	++	Died 3 days	Abscess between tumor and abdominal wall. Peritonitis. Sarcoma arising in endome- trium with extension to pelvis
++	++	+	+	++	-	Died 4 mo.	Operation was dilatation and curettage and excision of tumor in cul-de-sac. Radium in uterus. Liver metastases
+++	+	+	-	+	+	Well 6 yr.	Radium in cervix
++	++	+	++	+	-	Died 15 mo.	Examination negative and apparently well 9 mo. postoperative. Cause of death sarcoma?
++	+	+	+	+	-	Died 17 mo.	Previous hysterectomy for large adeno- fibroma. Operation this time was biopsy of cervix and excision of metastasis from right axilla. Radium in cervix. Chest metastases on x-ray
++	+	+	-	+	-	Well 5 yr.	Radium in cervix
++	++	+	++	++	+	Well 5 yr.	
++	++	+	++	++	+	Well 6½ yr.	Pedunculated tumor of endometrial cavity
++	++	+	+	+	-	Well 5 yr.	Associated with adenomyoma uteri
++	+	+	+	+	-	Well 6 yr.	
++	+	+	-	++	-	Died 10 mo.	Cervical leiomyosarcoma 2 yr. ago. Re- moval of large pedunculated tumor of cervix and radium inserted 9 mo. ago. Recurrence excised from pelvis this time.
+++	+++	++	+	+++	++	Died 22 mo.	Sarcoma arising in endometrial polyp, cause of death. Exam. 15 mo. after operation neg. for tumor but had hypertension, hyperthyroidism, and mitral insufficiency
++	++	++	+	++	+	Well 4 yr.	Case reported previously. ⁴ Mixture of sar- coma and adeno- and squamous cell car- cinomas in endometrial polyp
+++	++	+++	+	++	++	Died 12 days	Tumor tight in pelvis and hard to remove. Intestinal obstruction cause of death
+++	++	++	+	+++	+	Alive 3½ yr.	Had nodules in abdominal wall few months after operation; these went away under treatment. Definite recurrence of old sarcoma of uterus in abdominal wall for past year
+++	++	++	+	++	+	Well 3 yr.	
++	++	+	++	++	-	Well 2 yr.	
+++	+++	++	++	++	+	Died 6 mo.	Metastases to Fallopian tube and another fibroid

designations apply to microscopic characteristics of tumors.)

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EFFECTS OF ESTROGENIC THERAPY UPON OVARIAN FUNCTION

I. When Employed During Normal Menstrual Cycles

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A GENERALLY accepted concept of endocrinology is that the function of a gland is not stimulated but rather is depressed by its own intrinsic secretion. This concept has been held applicable both to adequately and inadequately functioning glands.

Two considerations were responsible for these investigations of the effects of estrogenic therapy upon the functional levels of ovaries: (1) The present widespread, contraphysiologic usage of estrogens in women in whom no proved ovarian failures exist, suggested the need for a clearer definition of the after effects of this empiricism. (2) The fact that recovery of full ovarian function results in a goodly number of women who had had prolonged or excessive estrogenic bleeding and who had been treated with a cyclic estrogen-progesterone schedule,¹ raised the question whether or not direct ovarian stimulation had occurred from what appeared to be essentially a complementary or substitutional regime.

The present communication is concerned with analyses of the effects of hormonal and nonhormonal estrogens upon the normal ovarian function which is characterized by cyclic bleeding from progestational endometriums. The subsequent and second communication² of this series deals with the effects of estrogenic therapy upon anovulatory ovarian failure, wherein relatively cyclic episodes of estrogenic bleeding occurred.

Methods

This investigation concerns 30 healthy women who bled from progestational endometriums. Their ages ranged from 16 to 35 years, and averaged 24.7 years.

Four estrogens (3 hormonal and 1 nonhormonal) were employed: estradiol in the forms of its esters, the benzoate,* and the dipropion-

*Estradiol benzoate (progynon-B) supplied by Schering Corporation, Bloomfield, N. J.

In view of the importance of finding evidence of invasiveness in these tumors, careful examination of the gross specimen as well as the periphery of the tumor microscopically should be done in all cases.

It is of incidental interest in this series of 27 cases that 3 of the tumors were a mixture of sarcoma and carcinoma and a fourth case was associated with a papillary cystadenocarcinoma of the ovary. Only two of the 27 patients were negroes. The average age at operation was somewhat over fifty-one years, with the youngest thirty years and the oldest sixty-eight. A rather striking feature is that only 1 of the 12 patients under fifty years of age at the time of operation has died, whereas only 1 of the 15 patients over fifty at the time of operation is alive and well. The average number of pregnancies, when this information was given, was about 3, although 6 of the 20 had had no children. Sixteen of the patients had reached the menopause at the time of operation, while 10 were still menstruating. Eighteen of 26 patients had had abnormal vaginal bleeding; 17 of the 26 had had pain; and 12 of 18, in which this information was given, had had abdominal swelling or tumor, as preoperative symptoms. Deep x-ray therapy following operation appears to have had no strikingly beneficial effect on the course of the tumors in this series, since 8 of the 15 patients receiving it have died with sarcoma or have had recurrence. Three of 9 patients that had had panhysterectomies are known to have died with sarcoma or have had recurrence. On the other hand, only 4 of 15 patients that had supravaginal hysterectomies as treatment for sarcoma have died with sarcoma or have had recurrence. This suggests that the type of hysterectomy was not an important factor in prognosis in most of the cases.

Summary and Conclusions

A study of 27 cases diagnosed sarcoma of the uterus is presented. It appears from this study that the gross or microscopic evidence of invasiveness in uterine connective tissue neoplasms is a very important criterion of the malignancy of these tumors, whereas the microscopic features such as increase in cellularity, variability in cellular morphology, anaplasia, giant cells, hyperchromatic nuclei, and even mitoses, are not nearly as reliable as criteria of malignancy; in fact, these findings were quite misleading in a considerable number of cases of this series. Unless there is evidence that the tumor is invasive, it seems advisable not to make the diagnosis of sarcoma.

Whereas only 25 per cent of the so-called sarcomas arising in fibroids were proved to be malignant. Nearly 55 per cent of those not arising in fibroids were proved to be malignant. The ratio of the diagnosis of sarcoma uteri to that of fibroid uteri in the period covered by this report was approximately 2 per cent.

Only one patient under fifty years of age at the time of operation has died, whereas only one patient over fifty years of age at operation is alive and well.

TABLE I. CLINICAL DATA IN REGARD TO ESTROGENIC THERAPY AND ENDOMETRIAL RESPONSES

		PATIENTS	CYCLES	ENDOMETRIAL BIOPSIES	
				ESTROGENIC	PROGESTA-TIONAL
Estrone:					
0.2 mg. 5th to 14th day inclusive	3	4	0	3	
0.4 mg. 5th to 14th day inclusive	7	10	0	7	
0.2 mg. 15th to 24th day inclusive	4	4	0	2	
0.4 mg. 15th to 24th day inclusive	1	1	0	0	
Summary:		19	0	12	
Estradiol benzoate:					
0.33 mg. 5th to 14th day inclusive	1	3	1	1	
0.67 mg. 5th to 14th day inclusive	4	4	1	1	
Summary:		7	2	2	
Estradiol dipropionate:					
1.5 mg. 5th to 14th day inclusive	5	11	4	3	
1.5 mg. 15th to 24th day inclusive	1	1	0	1	
Summary:		12	4	4	
Estriol glucuronide:					
1800 o.u. 5th to 14th day inclusive	1	1	0	1	
450 o.u. 5th to 24th day inclusive	1	1	0	0	
900 o.u. 5th to 24th day inclusive	2	3	0	0	
1800 o.u. 5th to 24th day inclusive	3	3	0	1	
2400 o.u. 5th to 24th day inclusive	2	4	0	0	
900 o.u. 15th to 24th day inclusive	1	1	0	0	
1800 o.u. 15th to 24th day inclusive	1	1	0	0	
Summary:		14	0	2	
Diethylstilbestrol:					
1 mg. 5th to 14th day inclusive	10	26	9	5	
2 mg. 5th to 14th day inclusive	1	1	1	0	
6 mg. 5th to 14th day inclusive	1	1	0	0	
1 mg. 5th to 24th day inclusive	1	1	0	0	
2 mg. 5th to 24th day inclusive	1	1	0	0	
3 mg. 5th to 24th day inclusive	1	2	0	0	
Summary:		32	10	5	
Total: 84 cycles of therapy; 41 biopsies studied, 16 estrogenic and 25 progestational.					

dipropionate therapy occurred under circumstances wherein the cycle length was doubled; accordingly, this response, being only remotely related to therapy, is regarded as having been the result of post-therapy recovery.) The one cycle in which therapy with the dipropionate was given during the latter half (fifteenth to twenty-fourth day) was characterized by the occurrence of a progestational endometrium. Progestational endometriums were encountered during 12, or 85.7 per cent, of the 14 first treatment cycles in which the endometrium was studied and during 77.7 per cent of the second treatment cycles.

Subsequent to the cessation of therapy endometrial studies were made on 5 patients (4 patients who had had single cycles of therapy and one patient who had had 4 consecutive cycles of therapy) during a total of 8 cycles. Eighty-seven and one-half per cent of these endometriums was progestational. The only estrogenic response occurred in a patient whose last therapy (2 cycles previously) had embraced the use of estradiol dipropionate.

B. Nonhormonal Estrogen (Diethylstilbestrol): The endometrial responses were studied in 15 of the 32 cycles of treatment with diethylstilbestrol of 9 of the 13 patients. Sixty-six and seven-tenths per cent

ate;* estrone;† estriol glucuronide;‡ and diethylstilbestrol.§ Estradiol and estrone were administered intramuscularly in oil. Estriol glucuronide and diethylstilbestrol were given orally.

Daily dosages were moderately small: estradiol benzoate 0.33 mg. to 0.67 mg.; estradiol dipropionate 1.5 mg.; estriol glucuronide 450 oral units to 2,400 oral units; and diethylstilbestrol 1 to 6 mg. Sixty-one cycles of therapy were administered during the first half of the ovarian cycle, i.e., from the fifth to the fourteenth day inclusive. Fifteen cycles of treatment extended from the fifth to the twenty-fourth day inclusive. Eight cycles of treatment were given during the last half of the cycle, i.e., from the fifteenth to the twenty-fourth day inclusive.

Fifteen patients received therapy during single cycles; 10 patients during 2 consecutive cycles; 7 patients during 3 consecutive cycles; 3 patients during 4 consecutive cycles; and 1 patient received therapy during 5 consecutive cycles.

Endometrial studies were made prior to, during, and after the cessation of treatment. Endometrial samples were taken by biopsy within the first twenty-four hours after the onsets of bleeding. Classification of the endometria was done by one of us (E. C. H.).

Data upon the lengths of the cycles, and the durations and amounts of bleeding episodes before, during, and following therapy were analyzed.

The urinary excretions of sodium pregnanediol glucuronide of 9 patients before and during treatment were investigated by the method of Venning.³

All patients received complete medical, gynecologic, and endocrine surveys which included determinations of basal metabolic rates and roentgenograms of the sella turcica.

Data

Therapy was administered during 84 ovarian cycles. Following cessation of therapy clinical data were obtained upon 72 additional cycles. In all a total of 156 cycles was studied.

Dosage Schedules.—The estrogens employed, their daily doses, the days of treatment in relation to the bleeding cycles, and the endometrial responses resulting are presented in Table I.

1. *Effects Upon the Endometrium.*—A. *Hormonal Estrogens:* The endometrial responses were studied during 26 of the 52 cycles of treatment of 16 of 19 patients who received hormonal estrogens. Six of the 26 endometrial responses were estrogenic; all of these were associated with therapy with estradiol. All endometria studied during cycles treated with estrone and estriol glucuronide were progestational. Estradiol was given during the first half of the cycle (fifth to fourteenth day) in 18 of the 19 cycles of therapy: 11 cycles of treatment employed the dipropionate and 7 the benzoate. Endometrial responses were studied in 11 of these cycles. Use of the benzoate yielded 2 estrogenic and 2 progestational endometria, and the dipropionate 4 estrogenic and 3 progestational. (One of the progestational responses related to estradiol

*Estradiol dipropionate (di-ovoclyn) supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

†Estrone (theelin) supplied by Parke, Davis and Company, Detroit, Michigan.

‡Estriol glucuronide (emmenin) and

§Diethylstilbestrol (estrobene) supplied by Ayerst, McKenna and Harrison, Ltd., Rouses Point, N. Y.

TABLE II. ENDOMETRIAL RESPONSES DURING AND AFTER THERAPY*

CASE NO.	SERIES OF THERAPY	CONSECUTIVE CYCLES STUDIED									
		1	2	3	4	5	6	7	8	9	10
1	1	e-M	es-M+	edd-E	edd-P	ORx-P					
2	2	edd-E	ORx-O								
3	1	e-M	e-M								
4	1	e-M	e-M	ORx-O							
5	1	e-M									
6	1	edb-M									
	1	edd-E	ORx-O	ORx-E							
	2	e-O	ORx-M-								
	3	e-O	ORx-M								
	4	edd-O	ORx-O								
7	1	e-M	es-O								
8	1	e-M	es-M	ORx-O	ORx-O	ORx-M+	ORx-O	ORx-O	ORx-O	ORx-O	
	2	es-O	ORx-O	ORx-O	ORx-P						
9	1	edd-M	edb-E	edd-O							
10	1	e-M	e-M	e-O	ORx-O	ORx-O					
	2	e-O	ORx-O	ORx-O							
	3	es-O	ORx-O								

*Therapy

edd, Estradiol dipropionate
 edb, Estradiol benzoate
 e, Estrone
 es, Estril
 glucuronide
 stb, Diethylstilbestrol

ORx, No therapy, but data on cycle and bleeding obtained

Classification of Endometrial Responses

E, Moderate estrogenic response
 E+, Marked or hyperestrogenic response
 M-, Minimal, irregular (patchy) progesterone
 M, Moderate, irregular (patchy) progesterone
 M+, Marked, irregular (patchy) progesterone
 P-, Minimal (immature) regular progesterone
 P, Normal progesterone
 P+, Marked (deciduallike) progesterone
 O, No biopsy

of the endometriums were estrogenic. Following cessation of treatment endometrial studies were made during 11 cycles of 3 patients whose previous therapy had extended over 2 to 4 cycles: 2 endometriums were estrogenic and 9 were progestational, 18.2 per cent and 81.8 per cent, respectively.

Table II summarizes the endometrial responses during and after therapy.

2. *Effects Upon the Lengths of the Cycles.*—A. *Hormonal Estrogens:* There were no significant alterations either during or following therapy with estrone or estriol glucuronide. The cycles during treatment with estradiol benzoate and dipropionate were shortened in length with two exceptions; with estradiol benzoate from 29.5 days to 24.7 days, and estradiol dipropionate from 32.2 days to 26.5 days. The average deviation of the treatment cycle lengths from the pretreatment cycle lengths was, however, -3.1 days for the benzoate and -7.1 days for the dipropionate. Following the cessation of therapy, the cycles were of usual pretreatment lengths. In the cases of the 2 exceptions mentioned, estradiol therapy was followed by the absence of the expected episodes of bleeding with sequential doubling in the lengths of the cycles.

B. *Nonhormonal Estrogen (Diethylstilbestrol):* Without relationship to dosage or to the time of the cycle during which diethylstilbestrol was administered, the lengths of treatment cycles were altered in the majority of instances. The cycles of 5 patients were shortened from an average length of 29.6 days to one of 20.3 days. The cycles of 2 patients were lengthened from 25.4 days to 38.2 days. The lengths of the cycles of 5 patients were not altered constantly in any direction. No significant changes occurred in the lengths of the cycles of 1 patient. After cessation of treatment, cycles returned to their usual lengths. Only one episode of uterine bleeding occurred concomitantly with therapy.

3. *Effects Upon the Duration and Amount of Bleeding.*—A. *Hormonal Estrogens:* The duration of bleeding was not altered significantly during or after therapy with estradiol benzoate or estriol glucuronide. The alterations following employment of the other estrogens were not marked. Following treatment with estrone, the average duration of bleeding was reduced from 6.6 days prior to therapy to 5.0 days during and 4.4 days following cessation of treatment. Following treatment with estradiol dipropionate, the average duration of bleeding was increased from 4.6 days prior to therapy to 5.3 days during treatment, and 3.4 days following cessation of treatment. No marked alterations occurred in the amounts of bleeding during therapy or subsequent to its cessation.

B. *Nonhormonal Estrogen (Diethylstilbestrol):* Following therapy with diethylstilbestrol the duration and the amount of bleeding tended to parallel the changes in the lengths of the cycles.

4. *Effects Upon Withdrawal Time.*—The criterion employed for withdrawal bleeding was the occurrence of episodes of bleeding within a few days after cessations of therapy, and considerably in advance of expected dates of bleeding.

A. *Hormonal Estrogens:* No instance of withdrawal bleeding followed therapy with hormonal estrogens.

B. *Nonhormonal Estrogen (Diethylstilbestrol):* The withdrawal times could be evaluated in 14 cycles of 7 patients. They ranged from two to eight days, the average being six days. The average length of the involved cycles was 19.5 days.

5. *Effects Upon the Urinary Excretion of Sodium Pregnanediol Glucuronide.*—A. *Hormonal Estrogens:* The urinary sodium pregnanediol

glucuronide excretions of 3 patients prior to and during treatment were determined. The amounts excreted prior to therapy were 36 mg., 29 mg., and 0.0 mg., respectively, and during treatment 53 mg., 14 mg., and 17 mg., respectively. The patient who excreted 14 mg. of the pregnanediol complex during therapy bled from an estrogenic endometrium at the termination of that particular cycle. The number of determinations per patient cycle averaged 18 prior to therapy and 17 during therapy.

B. *Nonhormonal Estrogen (Diethylstilbestrol)*: Levels of sodium pregnanediol glucuronide excretion of 6 patients were established prior to and during treatment. Only 2 patients excreted the pregnanediol complex prior to therapy and none during therapy. Estrogenic endometriums terminated three of these treatment cycles. The number of determinations per patient cycle averaged 13 prior to therapy and 19 during treatment.

Discussion

The contraphysiologic employment of moderately small doses of hormonal and nonhormonal estrogens in women with normal ovarian function produced definite effects upon the menstrual cycle.

As a group, the hormonal estrogens exerted little depressing effect upon corpus luteum function. Estradiol dipropionate, however, which was given in the largest amounts, yielded definitely depressing effects. The group percentage of estrogenic endometriums during therapy was 16.7 while in the instance of estradiol dipropionate it was grossly 50 per cent, and on analysis 66.7 per cent.

Diethylstilbestrol, even in the small amounts used, also depressed corpus luteum function. During therapy with this estrogen 66.7 per cent of all the endometrial responses studied were estrogenic while 62.5 per cent of the endometriums at the termination of the first treatment cycles were estrogenic.

Milligram for milligram diethylstilbestrol was given in larger daily doses than the hormonal estrogens. In those cycles, however, in which therapy was given during the first half (fifth to fourteenth day) and from which most of the endometrial data were obtained, diethylstilbestrol was given in amounts of 1 to 2 mg. daily and estradiol in amounts of 1.5 mg. daily. Not only were the doses in milligrams similar but also the effects on corpus luteum function were similar, 66.7 per cent depression in each instance. The fact that these effects were observed with the two estrogens which were given in largest amounts makes it probable that use of the other estrogens would have yielded similar results if comparable doses had been employed.

The relative potencies of the various estrogens remain, as yet, controversial. From our data it appears that diethylstilbestrol in daily doses of 1.0 mg. during the first half of the cycle is as effective in depressing corpus luteum function as 1.5 mg. of estradiol dipropionate. From other work by our group not yet reported and from the literature Table III,⁴ which summarizes relative potencies, has been compiled.

therapy most certainly is metabolized and it is impossible to conceive of a lack in the amount of available estrogen. Ovulation is not a factor in cycle length because the cycles were shortened whether ovulations and progestational responses occurred or not. The cycle lengths were not shortened, as a rule, to the extent that a withdrawal effect could be postulated. A possible explanation is that the increased supply of estrogen causes more rapid proliferation and maturation of the endometrium with a decrease in length of the estrogenic phase of the cycle. The entire effects of therapy on the cycle lengths, therefore, doubtlessly occur at the endometrial level.

Diethylstilbestrol therapy produced a number of effects on cycle lengths. The cycles of some patients were shortened while others were lengthened. In general, those patients whose cycle lengths were long before treatment were shortened during treatment, and those which were short before treatment were lengthened during treatment. Of the group of 5 patients who had changes in both directions, the average cycle length before treatment was 28.0 days and the average deviation of all cycles during treatment was +4.6 days. This shows a significant trend toward lengthening. There is no correlation of these variations with dosage, and there is no obvious explanation for them. It is also interesting but not explained that the duration of bleeding episodes should vary with the changes in cycle lengths.

Despite the fact that no persistent ill effects of therapy have been encountered, these findings do not warrant any conclusions with regard to the ultimate results that might follow protracted therapy with larger doses of either hormonal or nonhormonal estrogens.

Summary and Conclusions

Moderately small doses of hormonal estrogens (estrone, estradiol benzoate and dipropionate, and estriol glucuronide) and of a non-hormonal estrogen (diethylstilbestrol) were administered contraphysiologically to 30 women who had normal ovarian function. The hormonal estrogens, with the exception of estradiol dipropionate, had no depressing effect upon corpus luteum function, presumably because of insufficient dosage. Estradiol dipropionate which was given in larger dosages produced definite depression of corpus luteum function which was equal in degree to the depression produced during therapy with diethylstilbestrol. Both of these estrogens were given in similar doses in terms of milligrams and each produced depression of corpus luteum function in 66.7 per cent of the treatment cycles.

Definite and quantitative alterations in the menstrual cycle were observed during therapy with those estrogens which were given in larger doses. The changes with diethylstilbestrol were marked by their lack of uniformity.

TABLE III. RELATIVE POTENCIES OF ESTROGENS IN THE HUMAN FEMALE

CRITERIA	RELATIVE POTENCIES
1. Depression of corpus luteum function	1.0 mg. estradiol = 3.0 mg. estrone = 0.67 mg. diethylstilbestrol or on the basis of effective dosage 1.5 mg. estradiol = 4.5 mg. estrone = 1.0 mg. diethylstilbestrol
2. Vaginal smears*	1.0 mg. estradiol = 2.4 mg. estrone = 1.2 mg. diethylstilbestrol
3. Hemostasis	1.0 mg. estradiol = 3.0 mg. estrone = 5 to 6 mg. diethylstilbestrol (daily doses)
4. Manufacturer's claims*	1.0 mg. estradiol = 5.8 mg. estrone = 2.3 mg. diethylstilbestrol

*Stoddard and Metzger: J. Clin. Endocrinology 2: 209, 1942.

Following cessation of therapy with the hormonal estrogens, progestational endometriums were encountered in 87.5 per cent of the cycles. One of the patients who had progestational endometriums following cessation of treatment, had had 4 consecutive cycles of therapy. Following discontinuation of therapy with diethylstilbestrol 80 per cent of the endometriums was progestational. Thus, no permanent depressions of ovarian function followed therapy of the order given by us. Larger dosages of estrogens and more prolonged therapies might alter this finding. The modus operandi of the temporary impairment of ovarian function described is probably one of pituitary depression.

Therapy with estradiol benzoate and dipropionate was associated with shortening of the cycle lengths as is shown by the gross averages and the average deviations. Haman⁵ in a recent article computed the standard deviation of the normal cycle to be ± 2.2 days. Our average deviations were -7.1 days for estradiol dipropionate and -3.1 days for the benzoate. It is apparent that the effect of the benzoate was hardly significant while that of the dipropionate is quite significant. Here again the difference in effect is in all probability due to the employment of larger doses of the dipropionate. That there were no changes in the cycle lengths during therapy with estrone and estriol glucuronide is probably due to the smaller doses used.

Since it is the estrogenic phase of the cycle which determines cycle length, the shortening of the cycle lengths during therapy with estradiol dipropionate would presumably be explained on the basis of depression of ovarian function, the occurrence of which has been established by the reversed endometrial responses during therapy. The assumption that shortening of the cycle lengths is due to decreased ovarian function, and thereby a decreased production of estrogens, does not hold true. Such an assumption is similar to saying that a short menstrual cycle is indicative of a low level of ovarian function and a long cycle of a high level of function. The additional supply of estrogen given as

Hamblen,³ however, found not only marked variations of pregnanediol excretion in women with normal menstrual cycles, but also, that excretion was not continuous throughout the luteal phase of the cycle. More recently Cope⁴ concluded that pregnanediol excretion does not provide a reliable estimate of the intensity of corpus luteum metabolism. These, and many other divergent opinions on various phases of the problem prompted our present study.

Our purpose in this investigation is an attempt to evaluate pregnanediol excretion as a diagnostic index of ovarian and uterine function.

Methods and Materials

For this purpose, titrations of sodium pregnanediol glucuronide were estimated according to the gravimetric method of Venning.⁵ Twenty-four-hour samples of urine were collected on consecutive days and extractions of conjugated pregnanediol were estimated within twenty-four hours of the end of each collection period. No preservatives were used. Specimens were refrigerated to prevent hydrolysis. The purity of the final precipitate was checked by melting point determinations in each instance and only those with melting points between 268 and 271° C. were accepted.

As had been pointed out by Venning,⁵ considerable losses occur in the separation of small amounts of this material. The loss appears to be largely due to solubility and is therefore more nearly a constant absolute amount than a constant percentage of the amount recovered. Since no correction for this loss has been made in our data, the values must be looked upon as relative, rather than absolute. In this investigation, titrations were estimated on the following groups of women:

1. Controls:

- a. 4 with normal menstrual cycles
- b. 3 with primary sterility and normal cycles

2. Before and after hormone administration:

- a. 6 with amenorrhea (three primary and three secondary)
- b. 4 with cyclic anovulatory menstruation
- c. 1 case of secondary sterility (two previous abortions) and normal cycles
- d. 1 with bilateral salpingo-oophorectomy, uterus intact
- e. 1 with supracervical hysterectomy, ovaries intact
- f. 1 with complete vaginal hysterectomy, ovaries intact
- g. 1 with panhysterectomy

- 3. Endometrial biopsies were concurrently performed in an attempt to correlate these findings.

Results

Normals.—Four normal women were studied for a total of 14 menstrual cycles. Pregnanediol complex excretion varied from 21 to 64 mg. per cycle. Fig. 1 represents four typical cycles of one of the subjects in this group. No two like amounts were found in the same patient in successive cycles, nor was the duration of the excretion the same. In several instances, although pregnanediol could not be isolated on certain days, it did reappear later in the luteal phase. From the amount excreted, one could not prognosticate the interval or the duration of the

The following conclusions seem warranted:

1. Certain hormonal estrogens (estradiol) if given intramuscularly in adequate amounts will depress corpus luteum function.
2. Diethylstilbestrol, even in the moderately small amounts used by mouth, will depress corpus luteum function.
3. This depressing effect is not cumulative and does not persist after therapy.
4. The only direct effect of therapy on the ovarian level of function was the depression of corpus luteum function.
5. The other effects of therapy, i.e., on the cyclicity and duration of bleeding, probably resulted from action directly on the endometrium.

We acknowledge the cooperative aid of the group of healthy women studied. Part of the expenses of these studies was defrayed from grants to one of us (E. C. H.) from the Research Council of Duke University, from Ayerst, McKenna and Harrison, Ltd., Montreal, Canada, and from Schering Corporation, Bloomfield, N. J.

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(Section II of this paper will be published in the March issue.)

AN EVALUATION OF THE PREGNANEDIOL COMPLEX AS AN INDEX OF OVARIAN AND UTERINE FUNCTION

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THE corpus luteum and its hormones were early recognized as playing important roles in the complex metabolic and endocrine relationships in the human female. However, it was not until Marrian¹ isolated pregnanediol from the urine of pregnant women in 1929, that extensive studies were undertaken to elucidate the nature of its significance. Subsequently, Venning and Browne² contended that pregnanediol was a degradation product of progesterone and devised a method for its quantitative determination. Their studies indicated that pregnanediol was excreted only during the secretory phase of the menstrual cycle. It was suggested therefore that such determinations might afford both a valuable diagnostic index of ovulation and a gauge of the duration and functional activity of the corpus luteum.

change to an early secretory endometrium. It would appear that the Venning-Browne test is *complementary* to basal body temperature and endometrial biopsy studies in the determination of ovulation.

Primary Sterility.—Normal Menstruation: The 3 patients in this group had normal menstrual cycles and normal somatic findings. The complaint of sterility, however, brought them to our attention. Titration studies in this group yielded normal or diminished values, ranging from 16 to 45 mg. of pregnanediol complex per cycle. Endometrial biopsies

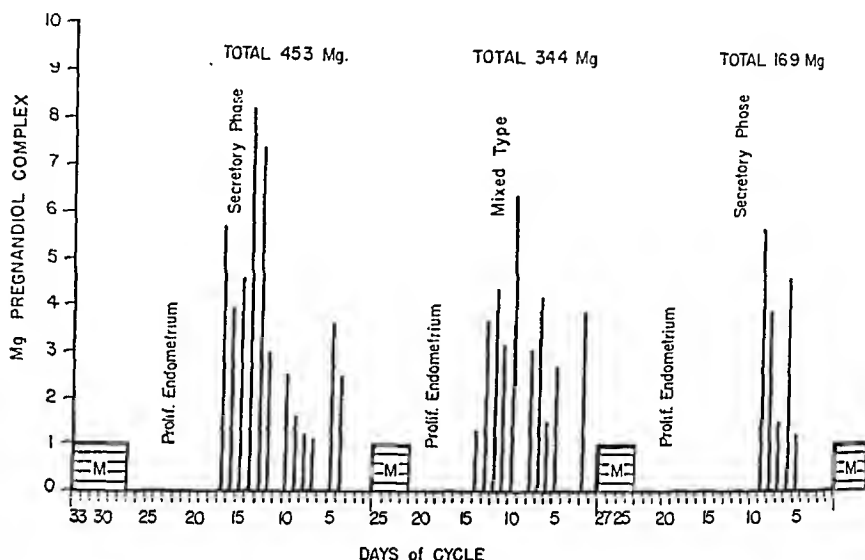


Fig. 3.—Three typical cycles in primary sterility.

revealed secretory or mixed types. Here again, as in the first group, pregnanediol excretion seemed to furnish a qualitative index of luteal activity but did not give a quantitative estimate of progesterone secreted, as evidenced by the lack of correlation with endometrial biopsies (Fig. 3).

Amenorrhea (Primary and Secondary) and Sterility.—Hypoplastic Endometrium: Titration studies on this group of 6 cases over a period of several months failed to yield any pregnanediol complex excretion and at no time did endometrial biopsies disclose a secretory phase of endometrium.

A study of the effect of administered hormones on this group is shown in Table I.

1. Estrolin, 10,000 I.U. daily, was given intramuseularly for fourteen consecutive days and was followed by progestin-in-oil, 5 mg. daily for seven days, with no resultant pregnanediol excretion. In two instances, vaginal bleeding resulted, and in both a secretory endometrial phase was found.

2. Estrolin, 10,000 I.U. daily for fourteen days, followed by combined estrolin (10,000 I.U.) and progestin-in-oil (5 mg.) daily for the next fourteen days, similarly yielded negative pregnanediol excretion. In all instances, vaginal bleeding resulted. Three cases showed a secretory endometrium, one a mixed type, and the remainder were proliferative.

3. Progestin, 10 mg. daily for five days, produced no effect on pregnanediol excretion. Vaginal bleeding occurred in two instances from a proliferative type of endometrium.

menstrual cycle. Fig. 2 represents the composite excretions of these 14 cycles. It was found that in no instance could any pregnanediol complex be isolated prior to the twelfth day of a twenty-four-day cycle, or the sixteenth day of a twenty-eight-day cycle. Moreover, there was no constant predictable excretion during a cycle. The greatest concentration occurred between the tenth and sixth days before the onset of menstrua-

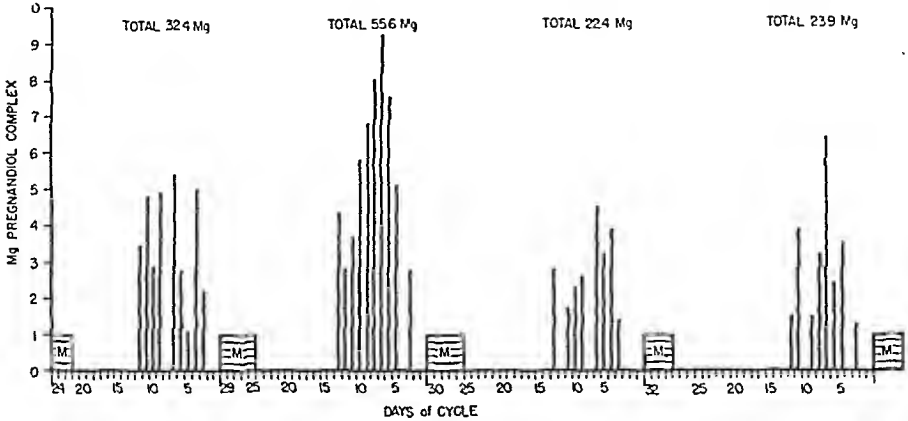


Fig. 1.—Four typical cycles of normal menstruation.

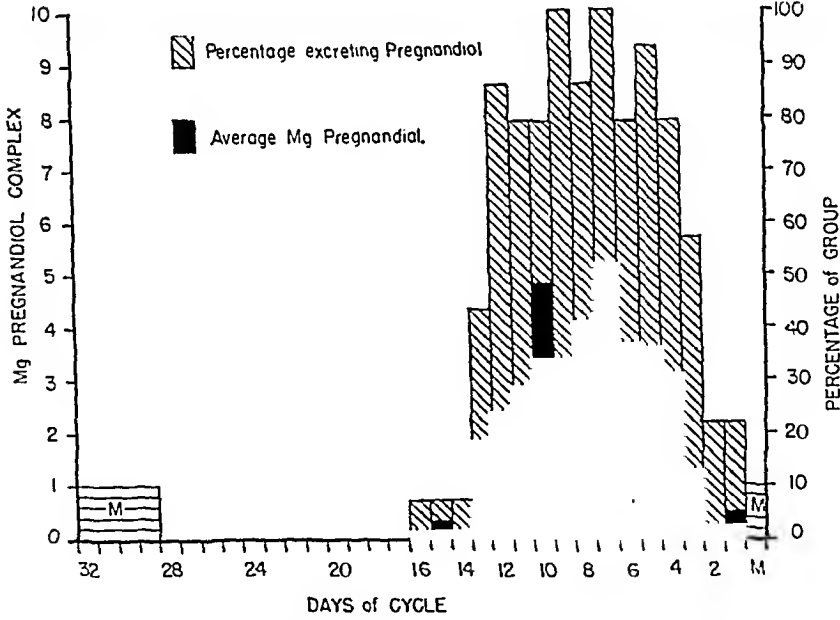


Fig. 2.—Composite graph of 14 normal menstrual cycles.

tion, and menstruation invariably occurred from none to three days following the disappearance of pregnanediol complex from the urine, regardless of its quantity or the duration of its excretion. It is likely that menstruation in all these instances was due to progesterone withdrawal. In three of these cases, endometrial biopsy and basal body temperature studies were concurrently done with urinary titration. In each instance, the first detectable appearance of pregnanediol complex occurred at the peak of the rise in temperature after the trough, with a coincidental

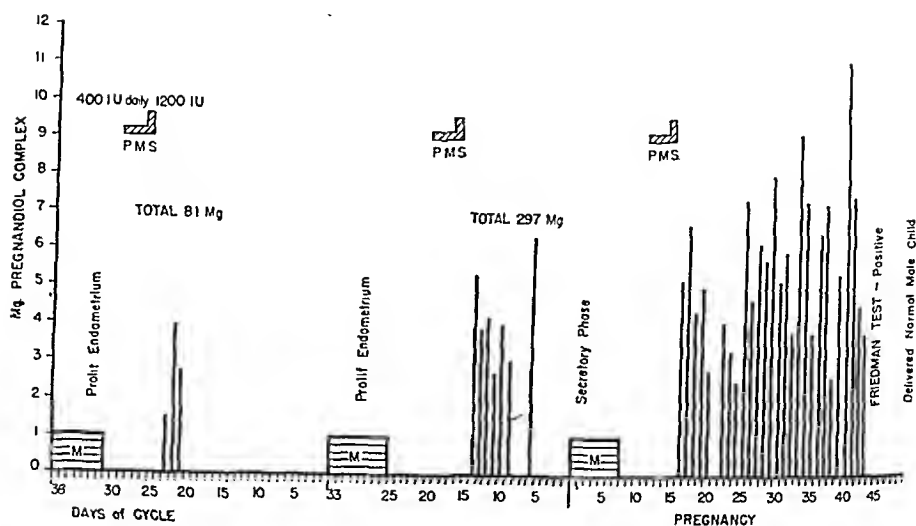


Fig. 4.—Anovulatory menstruation. Pregnant mares' serum therapy. Pregnancy.

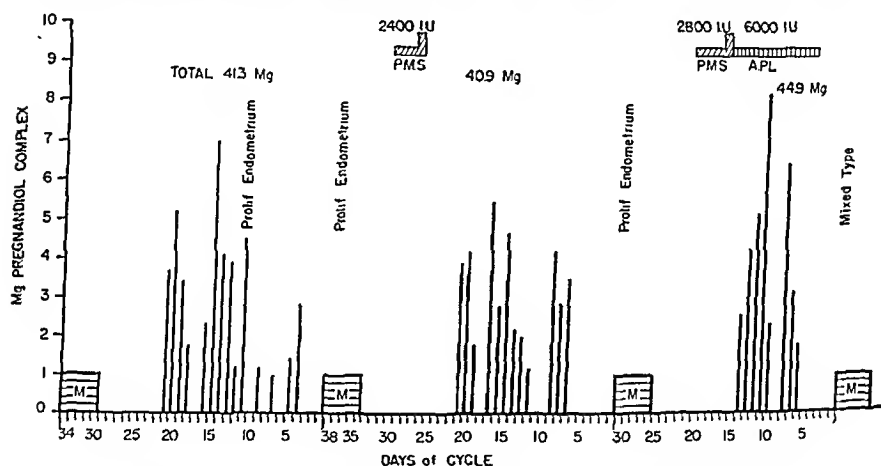


Fig. 5.—Primary sterility. Anovulatory menstruation. Pregnant mares' serum. Pregnant mares' serum and anterior pituitary-like hormone.

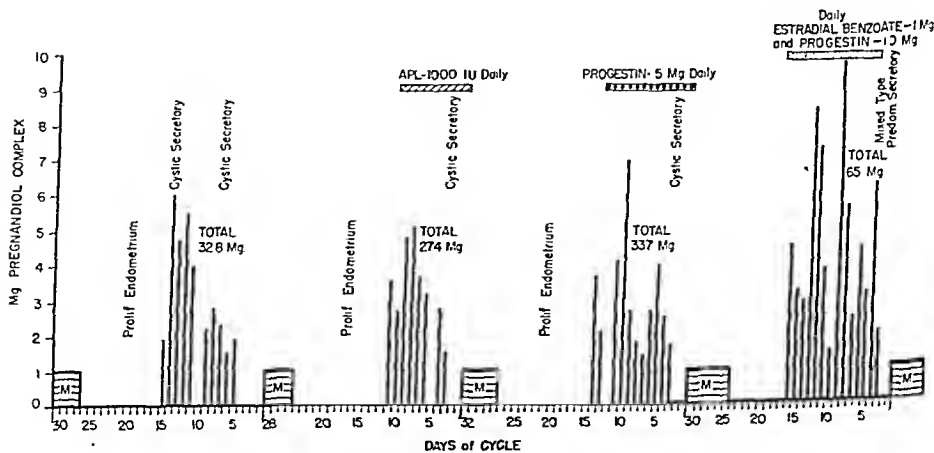


Fig. 6.—Secondary sterility with hormone therapy.

TABLE I

6 Cases of Amenorrhea: 3 primary and 3 secondary: Hypoplastic Endometrium

ESTROLIN I.U.	DOSAGE* PROGESTIN MG.	PERIOD OF TREATMENT (DAYS)	ENDOMETRIAL BIOPSY AT BLEEDING	PREGNANEDIOL EXCRETION
10 M → 5		E → P 14 → 7	3 cases, secretory	0
10 M → 10 M.E. + 5		E → E + P 14 → 14	3 cases, secretory 1 case, mixed 2 cases, proliferative	0
10		P 5	2 cases, proliferative	0
10 M → 10 M.E. + 10		E → E + P 14 → 14	6 cases, secretory	1 case, 6.1 mg.

*Estrolin, Lakeside Laboratories. Progestin-in-oil, Lakeside Laboratories.

4. Estrolin, 140,000 I.U. in daily divided doses, followed by combined estrolin (10,000 I.U.) and progestin (10 mg.) daily for fourteen days, had no effect on pregnanediol excretion in all but one case, having excreted 6.1 mg. Vaginal bleeding and secretory endometrial phases were noted in each instance.

These observations suggest that progesterone may be secreted in sufficient quantity to produce endometrial modifications and bleeding without the urinary excretion of pregnanediol, indicating that the threshold dose of progesterone required for endometrial stimulation is below that at which the hormone is excreted as pregnanediol. It is suggested also, that estrogen and progesterone are synergistic in action with respect to development of the progestational endometrium, particularly when they are simultaneously administered to an estrogen-primed endometrium.⁶

Anovulatory Cyclic Menstruation.—Four sterile women with anovulatory menstruations and proliferative, persistent, endometrial phases, were followed for several months to establish control records. Two thousand four hundred to 2,800 I.U. of pregnant mares' serum was then administered intravenously in divided doses to each of the subjects.

a. In two cases, with previously diminished pregnanediol complex excretion, pregnancy and progressively increasing pregnanediol excretion resulted (Fig. 4).

b. In one case, with previously absent pregnanediol excretion, the administration of pregnant mares' serum and anterior pituitary-like substance, alone, in combination, or in sequence, produced neither a change of endometrial phase nor pregnanediol excretion.

c. Pregnant mares' serum was without effect on endometrial phase and pregnanediol excretion in one patient with a previously normal pregnanediol excretion. The administration of pregnant mares' serum and anterior pituitary-like substance sequentially, produced a change to a mixed type of endometrium but no appreciable change in pregnanediol excretion (Fig. 5).

There was apparently no correlation between pregnanediol excretion and endometrial biopsy studies, for excretion varied from negative to normal values in the presence of a persistently proliferative endometrium.

Surgical Cases.—This group included 4 women who had been subjected to varying degrees of gynecologic surgery. After a control period, progesterin (120 to 150 mg.) was administered in daily divided doses, and urinary titration of pregnanediol complex was estimated in order to determine the amount recovered (Table II). It will be noted that hysterectomized women showed recoveries of 7.4 to 9.4 per cent. This study seems to indicate that the endometrium is not a necessary factor in the metabolism of progesterone and that the normal ovarian cycle was uninterrupted following hysterectomy when the ovaries were left in situ.

Discussion

Positive results are of greater significance than negative results, for cases that excrete large amounts of sodium pregnanediol glucuronide suggest the occurrence of cyclic ovarian function regardless of the type of endometrium found. Those patients that show a persistently negative excretion may be considered clinically as anovulatory, for we have not found a secretory phase of endometrium in any of our patients showing a persistently negative excretion.

Cases of primary and secondary amenorrhea, and functional cyclic bleeding with hypoplastic, proliferative and mixed types of endometrium, excreted from none to variable amounts of sodium pregnanediol glucuronide. A positive excretion does not always reflect progestational changes in the endometrium, for the endometrium may be refractory and thus not metabolize the progesterone to be used for progestational differentiation. On the other hand, if it is metabolizing, the endometrium may not have the ability to use the progesterone.

There seems to be no obvious reason to object to a concept that postulates the secretion of follicular, and later, luteal hormones by the same cells at different phases of a life cycle of secretory activity.⁷ Evidence is accumulating to show that large follicles may begin to change their secretion, perhaps toward the luteal type, before ovulation.⁸

A positive reaction, or the finding of conjugated pregnanediol may result not only from the postovulatory corpus luteum, or, as intimated by Zondek,⁹ from the production of minimal amounts of progesterone by the corpus luteum of the preceding menstrual cycle which is doubtful, but from several other possible sources: the luteinization of granulosa or theca cells of the follicles; theca of atretic follicles; accessory corpora lutea in large follicles that have not ovulated, or possibly, some metabolic condition within the adrenal cortex, producing substances, if not similar, at least closely related to pregnanediol.¹⁰⁻¹⁸

Replacement therapy with estrogens and progesterone had no effect on pregnanediol excretion or clinical picture, unless daily injections of large doses of the combined endocrines were given to an estrogen-primed uterus for at least fourteen days. When estrogen and progesterone were concurrently given to an estrogen-primed patient, a notable synergistic effect was produced. It would appear that estrogen augments

TABLE II. PREGNANEDIOL EXCRETION—OPERATIVE CASES

OPERATION		MG. PROGES- TERONE EX- CRETED CON- TROL PERIOD†	MG. PROGES- TERONE AD- MINISTERED	MG. PROGES- TERONE EX- CRETED	MG. % RECOVERY
M.E.	Bilateral salpingo- ophorectomy Uterus intact	0	1st day—30} 2nd day—30} 3rd day—30} 4th day—30} 5th day— 0}	6.1 5.3 <hr/> 11.4	9.5
*R.A.	Supracervical hysterectomy Ovaries intact	7.3	1st day—50} 2nd day—50} 3rd day—50} 4th day— 0}	14.4 4.0 <hr/> 18.4 7.3 <hr/> 11.1	7.4
†A.B.	Vaginal hysterec- tomy Ovaries intact	8	1st day—50} 2nd day—50} 3rd day—50} 4th day— 0}	11.8 7.6 <hr/> 19.4 8.0 <hr/> 11.4	7.6
I.B.	Panhysterectomy	0	1st day—50} 2nd day—50} 3rd day—50} 4th day— 0}	2.8 11.3 <hr/> 14.1	9.4

*R.A., Pregnanediol estimation, 7 months after operation.

†A.B., Pregnanediol estimation, 3 months after operation.

‡Factor 0.58 used in converting SPG to progesterone.

The action of pregnant mares' serum and anterior pituitary-like substance was variable and unpredictable.

Secondary Sterility (2 Previous Abortions).—Normal Menstruation: This patient was followed for two menstrual cycles, averaging 33 mg. of pregnanediol complex per cycle and cystic secretory endometrium (Fig. 6).

a. Ten thousand I.U. of anterior pituitary-like substance in equally divided daily doses in second half of cycle yielded no significant change in pregnanediol excretion or endometrium.

b. Progestin, 65 mg. in equally divided daily doses, was also without effect on pregnanediol excretion and endometrium.

c. Estradiol benzoate, 14 mg. together with 140 mg. of progestin in equally divided daily doses, was administered intramuscularly in the latter half of the cycle with resultant marked increase in pregnanediol excretion to 65 mg., and change of endometrium to the mixed type, predominantly secretory.

These studies suggest that anterior pituitary-like substance and progestin-in-oil have little effect when given alone, but when estrogen and progesterone are simultaneously administered, the metabolism of progesterone is enhanced, with effect on both pregnanediol excretion and progestational changes.

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ABSORPTION OF PROTEIN FROM THE VAGINA AND UTERINE CERVIX*

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ALTHOUGH absorption of drugs from the vagina has been studied by several workers, the absorption of proteins from the vagina and uterine cervix has not previously been demonstrated experimentally. In this report, absorption of peanut protein from the vagina and cervix was studied by a direct method,¹ which employed an immunologic technique.

There is abundant clinical evidence that absorption of drugs and chemicals from the vagina does occur. Cases have been reported of poisoning by bichloride of mercury, arsenic, belladonna, zinc sulfate, iodoform, and carbolic acid which were used in the vagina. These observations, however, do not differentiate between vaginal and cervical absorption.

Experimental work on drug absorption from the vagina has been done both in animals and human beings. Procedures for demonstrating absorption from the vagina have been based on pharmacologic and chemical principles. Macht^{2, 3} demonstrated the absorption of alkaloids, inorganic salts, esters, and antiseptics from the vagina in cats, dogs, and rabbits. Macht cites the work of Hamburger in 1876 as the first recorded experimental work in human beings on absorption from the vagina. Hamburger demonstrated the absorption of potassium iodide and potassium ferrocyanide. Robinson⁴ showed the absorption from the human vagina of potassium iodide, sodium salicylate, quinine hydrochloride, sucrose, and phenol red. In later experiments with dogs and

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the metabolism and utilization of progesterone when they are simultaneously administered.

Gonadotropic hormone, pregnant mares' serum, given alone or concurrently with anterior pituitary-like hormone, seemed to stimulate ovarian activity which was reflected in increased pregnanediol excretion and a change in endometrial architecture toward the secretory type. This change, however, was not consistent in all cases.

Summary and Conclusions

1. Sodium pregnanediol excretion was studied in women with normal menstrual cycles and in those with varying degrees of functional and organic gynecologic pathology with a view to an evaluation of the Venning-Browne test as a practical index of ovarian and uterine function. To aid in this evaluation, endometrial biopsies and the effects of the administered endoerines were also studied.

2. On the basis of our findings, we may conclude that pregnanediol excretion is not a positive index of ovulation nor of progesterone utilization and metabolism. While it is frequently complementary to endometrial biopsy and basal body temperature studies, the time-consuming nature of this test, together with the necessity of examining successive urinary specimens for ten to fourteen consecutive days in order to define a relative level of progesterone metabolism for one cycle, renders this method generally impracticable for diagnosis in clinical practice.

3. Estrogenic hormone augments the metabolism and utilization of progesterone when the hormones are simultaneously administered to an estrogen-primed uterus.

4. The action of gonadotropic hormones is not consistent in establishing biphasic ovarian response, as determined by the Venning test and endometrial biopsy studies.

5. The endometrium is not necessary for the metabolism of endogenous and exogenous progesterone.

6. It is possible that some at present undefined hormone influences, other than uterine, hepatic, or renal, will prove to be important in the metabolism of progesterone and pregnanediol excretion.

This study was aided by a grant from the Lakeside Laboratories of Milwaukee, Wisconsin, for which we express our gratitude. We also wish to thank them for the liberal supply of estrolin and progestin; the Upjohn Company for gonadogen, the hormone of pregnant mares' serum; and Ayerst, McKenna and Harrison for A.P.L. used in this investigation.

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Results

Twenty-one subjects were studied. They were ambulatory obstetric and gynecologic patients chosen at random from private practice. They were all married patients varying in age from 21 to 65 years. They included patients in various stages of pregnancy, cases of primary and secondary sterility, and also patients under postoperative and postpartum observation.

In four cases absorption from the cervix only was studied (Table I). Positive results were obtained in all cases. The absorption times in these patients varied from nine to sixteen minutes.

Seventeen cases were studied for absorption from the vagina (Table II). These subjects were observed for at least one hour and sometimes longer. If no reaction developed the patients were dismissed and instructed to return if any alteration in the site occurred. Of the 17 cases only 6 showed positive reactions (Table II). The absorption times in these cases varied from forty to one hundred and twenty minutes.

Of the 11 patients who failed to show the reaction at the end of the first hour, 9 were studied after varying intervals for absorption from the cervix (Table III). Five were tested at once for cervical absorption.

TABLE I. ABSORPTION OF PEANUT PROTEIN FROM THE UTERINE CERVIX

CASE	AGE	DIAGNOSIS	RESULT	ABSORPTION TIME IN MINUTES
4	30	Pregnancy, tenth week	Positive	12
5	50	Supracervical hysterectomy, sixth month postoperative	Positive	16
8	65	Third-degree prolapse of uterus	Positive	11
2	30	Cervical erosion	Positive	9

TABLE II.—ABSORPTION OF PEANUT PROTEIN FROM THE VAGINA

CASE	AGE	DIAGNOSIS	PERIOD OF OBSERVATION IN MINUTES	RESULT	ABSORPTION TIME IN MINUTES
1	41	Menopause	60	Negative	
6	21	Pregnancy, eleventh week	60	Negative	
10	49	Supracervical hysterectomy, eighteenth month postoperative	87	Positive	87
12	31	Secondary sterility	41	Positive	41
18	26	Pregnancy, eighth week	40	Positive	40
21	29	Sterility	60	Positive	120*
24	41	Functional amenorrhea	60	Positive	100*
25	22	Retroversion of uterus	56	Positive	56
9	37	No pathology	60	Negative	
13	26	Retroversion of uterus	60	Negative	
15	26	Sterility obesity	60	Negative	
16	34	Sterility	60	Negative	
17	24	Pregnancy, nineteenth week	60	Negative	
19	28	Pregnancy, fifteenth week	60	Negative	
22	49	Fibroid. Three months following radium therapy	60	Negative	
23	22	Four months post partum	60	Negative	
26	30	Sterility	240	Negative	

*Approximate time recorded by patient.

eats, Robinson⁵ surgically severed the vagina from the uterus and demonstrated the vaginal absorption of several drugs as well as of insulin and of pituitary extract.

The present investigation, which was performed in 1937, deals with the absorption of unaltered peanut protein from the human vagina and cervix. Peanut protein was selected because an appropriate serum for the study of this antigen was available.

Technique

The technique employed in the present study is a modification of that used by one of the authors¹ in studies of absorption of unaltered protein from the various parts of the gastrointestinal tract. It is based on the following immunologic principles: The skin of almost any individual can be passively and locally sensitized to a particular protein by the intracutaneous injection of a serum taken from a patient who is hypersensitive to that protein and who presents a marked skin reaction when tested with it. When this protein is fed orally, subsequent to the cutaneous sensitization, its entrance into the circulation is marked by a local reaction at the sensitized site characterized by pruritus, erythema, and wheal formation.

The technique for studying absorption of peanut protein from the cervix and vagina is as follows: The subject is passively and locally sensitized on the flexor surface of the forearm by an intracutaneous injection of 0.05 ml. of a 1-10 dilution of a serum containing reagins for peanut protein. This serum was obtained from a patient who developed severe allergic symptoms following the ingestion of peanut and who, when skin-tested with this antigen, manifested a marked cutaneous reaction to it. Nuts were excluded from the diet of the subject to be tested for a period starting twenty-four hours preceding the sensitization and lasting until the study was completed. Patients with hay fever, asthma, and other atopic illnesses were excluded from the study. Twenty-four or forty-eight hours after the subject was sensitized, she returned for the absorption test. For this a peanut preparation, consisting of 5 Gm. of raw ground peanuts in 15 ml. of water, was used.

For the purpose of studying absorption from the vagina, the cervix was covered with a metal cap, or occasionally with a rubber diaphragm. A gauze sponge saturated with the peanut solution was then inserted into the vagina with the aid of a bivalve speculum. The speculum was withdrawn, and the patient assumed a sitting position. The sensitized site was then watched for the onset of the reaction.

When cervical absorption was studied, a cotton applicator was dipped in the peanut solution and gently inserted for a distance of one-fourth to one-half inch into the cervical canal, where it was left in place. The patient was then reclining on the table.

Absorption of the peanut protein into the circulation was marked by the development of a local reaction at the sensitized site on the forearm. The onset of this reaction was usually ushered in by pruritus. This was immediately followed by an erythema which progressed to wheal formation. The absorption time was measured from the time of introduction of the peanut solution into the vagina or cervix to the first objective evidence of a reaction at the sensitized cutaneous site, namely erythema or wheal formation.

Absorption from the vagina proved to be more inconstant and slower than from the cervix, despite the fact that the area of exposed mucous membrane surface was larger and the amount of allergen employed was greater than in the cervical studies. Positive results were obtained in only 6 of the 17 cases studied and in these the absorption times were uniformly slow, varying from forty to one hundred twenty minutes.

The differences in absorption of protein from the vagina and cervix are not unexpected in view of the dissimilarities of the two surfaces. The cervical mucous membrane is made up of columnar, secreting epithelium, is rich in lymphatics, and is covered with an alkaline secretion. Such factors favor absorption. On the other hand, the vaginal mucous membrane is of the squamous type, is relatively poor in lymphatics and is covered with an acid secretion. These are properties which do not facilitate absorption.

In the use or administration of medicinal substances by the vaginal route for therapeutic, prophylactic, or hygienic reasons, the possibility that they may rapidly reach the blood stream should be kept in mind. Unless definite precautions are taken, medication intended for local effect in the vagina is likely to contact the cervix as well, and unanticipated rapid absorption may follow. Hence, it becomes necessary for the clinician to be mindful of the possible toxic properties of the medication employed and also of its potentialities as an antigen. The therapeutic agent may act as an excitant of an allergic reaction in an individual who is already sensitive to it or, as a result of single or repeated applications, it may actively sensitize the patient. In the light of the above observations, there is room for a more discriminating selection of materials which are commonly used for vaginal douches, tampons, suppositories, and for cervical treatments. On the other hand, when absorption is desirable, as in the vaginal administration of hormones, contact of the medication with the cervix should enhance the therapeutic effect.

Summary

1. A direct method of studying the absorption of protein from the human vagina and cervix has been presented.

2. Absorption of protein from the cervix is a normal phenomenon occurring in every case studied with peanut protein within a relatively short period, i.e., from eight to twenty-five minutes.

3. Absorption of protein from the vagina is inconstant. It occurred in this series in six out of seventeen cases. Absorption of peanut protein from the vagina is much slower than from the cervix, taking from forty to one hundred and twenty minutes.

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In all of these cases positive reactions resulted in from eight to thirteen minutes. It is possible that if a longer vaginal contact had been permitted some of these cases might have reacted during the second hour as occurred in Cases 21 and 24 (Table II).

TABLE III. ABSORPTION OF PEANUT PROTEIN FROM CERVIX IN CASES SHOWING NO ABSORPTION FROM THE VAGINA

CASE	AGE	DIAGNOSIS	RESULT OF VAGINAL ABSORPTION TEST	INTERVAL BETWEEN VAGINAL AND CERVICAL TESTS	RESULT	ABSORPTION TIME IN MINUTES
9	37	No pathology	Negative	48 hours	Positive	25
13	26	Retroversion of uterus	Negative	None*	Positive	11
15	26	Sterility, obesity	Negative	None*	Positive	11
16	34	Sterility	Negative	None*	Positive	13
17	24	Pregnancy, nineteenth week	Negative	None*	Positive	8
19	28	Pregnancy, fifteenth week	Negative	None*	Positive	9
22	49	Fibroid. Three months following radium therapy	Negative	24 hours	Positive	18
23	22	Four months post partum	Negative	24 hours	Positive	13
26	30	Sterility	Negative	4 hours	Positive	19

*Test performed at the completion of vaginal absorption test lasting one hour.

One case (26) which was negative after four hours of vaginal application was then tested for cervical absorption. A positive reaction resulted in nineteen minutes.

Three subjects (9, 22, 23) who showed no evidence of absorption from the vagina were tested for cervical absorption after an interval of from twenty-four to forty-eight hours. The absorption times in these cases were twenty-five, eighteen, and thirteen minutes, respectively.

Two cases which were negative on vaginal testing were not studied for cervical absorption.

Discussion

By means of the direct immunologic method employed it has been possible to detect almost immediately the absorption of peanut protein from the human vagina and cervix into the circulation. Previous studies indicate that the results obtained with peanut may be reproduced with almost any other protein for which a serum, suitable for study, can be found.

In every one of 19 subjects studied, peanut protein entered the circulation in from eight to twenty-five minutes after its application to the uterine cervix. Since most of these patients presented no pathology of the vagina or cervix, it is justifiable to assume that such absorption is a normal physiologic phenomenon.

While only minute traces of protein in the circulation are needed to light up the sensitized cutaneous site (studies with cottonseed extract have indicated that as little as 0.0001 mg. of nitrogen is required), such amounts may be sufficient to induce severe allergic reactions in individuals who are sensitive to these proteins.

That sequence of events is obvious to the pathologist and to the clinician before him. Indeed the observations of the latter may be essential to the correctness of the diagnosis as the anatomic interpretation is often difficult. The presence of amniotic fluid apart from cellular elements is not pathognomonic. Often, in fact, it cannot be differentiated histologically from pulmonary edema. Should death be delayed two or three days, a secondary or terminal pneumonia may obscure the primary disorder. The findings that warrant a diagnosis of asphyxia include chiefly the presence of desquamated amniotic epithelium, vernix caseosa, and lanugo hairs. Since these elements vary in amount from case to case and may occur in small quantities when death is attributable to some other cause, it must be repeated for the sake of emphasis that the diagnosis of intrauterine asphyxia rests not only on the pathologic findings but on the preliminary clinical evidence of respiratory obstruction.

An attempt to reduce the mortality rate of erythroblastosis fetalis by the prevention of asphyxia seems worthy of consideration. For many years, physicians have observed the tendency of the disease to make its appearance in successive pregnancies. The likelihood of recurrence is estimated at about 50 per cent. Investigations of recent years have shown that the predisposition to the disease may be explained on a hereditary basis. The newly discovered Rh blood factor in the fetus is regarded as a dominant mendelian characteristic. The nature of the inheritance is stated in terms of an isoimmunization theory which explains the maternal production of immune agglutinins and their subsequent passage through the placenta.

The mode of delivery to be employed in women who have previously given birth to an erythroblastic infant deserves emphasis; it represents a prophylactic point of attack. Analgesia and inhalation anesthesia are contraindicated. Since the incidence of intrauterine asphyxia varies directly with the duration of labor, the most rapid means of delivery is imperative. In such circumstances the justification for an elective cesarean section becomes absolute.

Among 8 cases recently observed, death with manifestations of asphyxia occurred in five. In three of these, the duration of labor exceeded ten hours and no evidence of interference with the supply of oxygen to the fetus was apparent. In another, labor lasted less than two hours, but delivery was complicated by hydramnios with prolapse of the cord. No records of the duration of labor were available in the fifth case delivered in a small maternity hospital. In 3 cases that survived, labor lasted ten hours or less.

It is apparent that the only safe way of avoiding a prolonged labor is to effect delivery by cesarean section. It should be performed under local anesthesia in order to eliminate the slightest disturbance from the anesthetic. Only statistics sufficiently ample will prove what now represents a reasonable assumption, namely, that a history of erythroblastosis fetalis justifies cesarean section.

THE RELATIONSHIP OF ERYTHROBLASTOSIS FETALIS TO INTRAUTERINE ASPHYXIA

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THE close relationship between universal edema of the fetus, icterus gravis neonatorum, and anemia of the newborn infant has become generally recognized since the publication of an article by Diamond and his associates in 1932. Accurate statistical data on these disorders is now available and accordingly the efficacy of therapy can be analyzed more readily. The immediate mortality in the entire group has been reduced since the use of blood transfusions but is estimated at the present time to be approximately 50 per cent. This seems surprisingly high when one observes how simply and completely recovery occurs in occasional cases in which the patient receives only a single transfusion. Diamond¹ rightly emphasized that the prognosis is in part dependent on the predominating symptom. Thus cases of universal edema have the least favorable outlook and next in order are the severely jaundiced infants. Theoretically, failure to respond to transfusions as evidenced by continued hemolysis may follow the use of blood from an Rh negative donor possessing anti-Rh antibodies. It is our conviction, however, that the high death rate is not due entirely to the severity of the disease per se nor to incompatible donors but in at least a fair number of cases to intrauterine asphyxia.

It is generally agreed that infants with erythroblastosis fetalis are particularly susceptible to asphyxia, presumably because of the reduced number of oxygen carriers. In a recent article Javert² states that fetal distress is frequently encountered and places the incidence as over 50 per cent. Additional evidence is contained in the autopsy protocols included in Diamond's paper. Intrauterine asphyxia may be suspected in some of the cases he described as aspirated vernix caseosa and amniotic fluid were found in the lungs.

So prominent are the clinical and laboratory findings which establish the diagnosis of erythroblastosis that the role assigned to asphyxia has been minimized or entirely overlooked. Once the diagnosis of erythroblastosis has been made, the physician seldom feels the need to look further. Moreover, complacency of this kind is favored by the fact that accompanying signs and symptoms usually attributed to erythroblastosis (pallor, listlessness, a feeble cry, subnormal temperature, inability to suck, abnormalities of respiration, and petechial hemorrhages) are likewise familiar characteristics of the asphyxiated infant.

As is well known, the most satisfactory evidence of intrauterine asphyxia relates to the aspiration of the amniotic fluid and its contents.

The alveoli contained large amounts of finely granular material which stains with eosin. There were occasional red cells, frequent epithelial squamæ and lanugo hairs (Fig. 1).

A bronchus contained large amounts of finely granular yellow brown pigment which did not give a reaction for iron and which was presumably meconium (Fig. 2).

CASE 2.—The child appeared critically ill at birth; respirations were shallow and labored and characterized by an expiratory grunt. The entry of air was greatly diminished and showers of râles were scattered over both lungs. The spleen and liver were palpable. The hemoglobin was 74 per cent; red blood count, 3,760,000; white blood count, 14,000; and nucleated red cells, 213 to 200 white cells. Clinical evidence of duodenal atresia was confirmed by autopsy. Blood transfusion, intravenous fluids, oxygen inhalation and supportive treatment maintained life for five days.

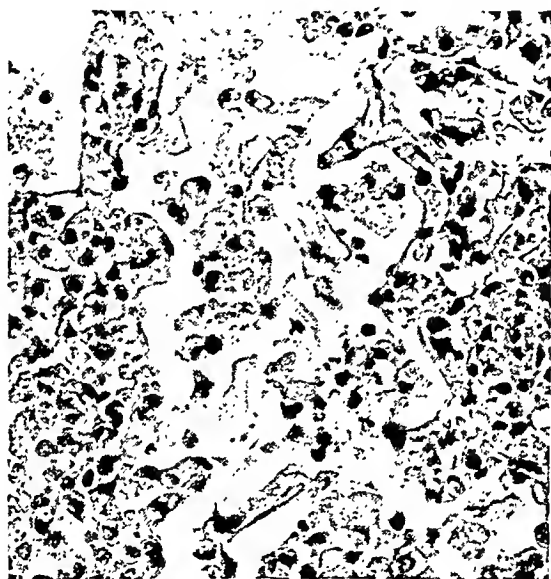


Fig. 3.

The lungs showed sharply outlined areas of necrosis in which the alveolar walls, bronchi, and vessels were largely destroyed. In these areas were large clumps of bacteria and much nuclear debris. The alveoli elsewhere contained granular material which stained with eosin, occasional neutrophils, and red cells. Frequent alveoli contained epithelial squamæ, and occasional lanugo hairs (Fig. 3).

CASE 3.—The child required resuscitation at birth and repeated inhalations of carbogen during the first day. Dyspnea subsequently developed; râles were present at the lung bases; and respirations ceased at the end of thirty hours. Jaundice and petechiae were noted during the first few hours. The hemoglobin was 30 per cent; red blood count, 990,000; white blood count, 22,200; 300 nucleated red cells to 200 white cells. Histologic examination of the lungs showed that the alveoli contained large amounts of granular and translucent material which stained with eosin, occasional polymorphonuclear cells and red cells. In one

Case Reports

CASE 1.—The infant showed jaundice and anemia as clinical evidence of erythroblastosis. The hemoglobin was 63 per cent; red blood count, 2,090,000; white blood count, 40,172; and erythroblasts, 597 to 100

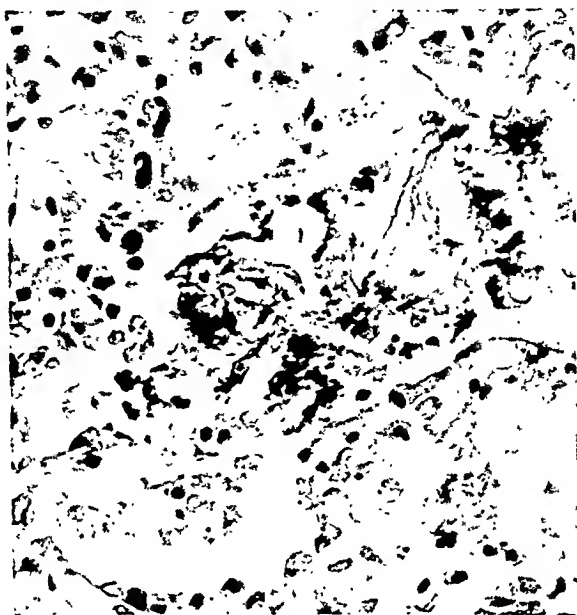


Fig. 1.

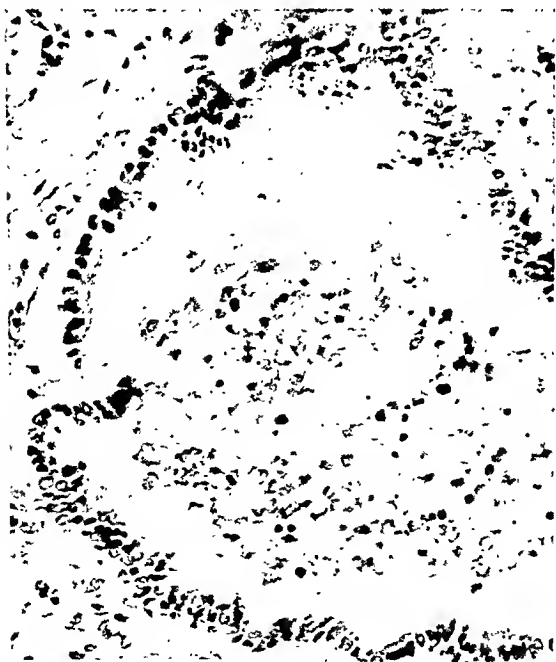


Fig. 2.

counted white cells. The respirations were labored and the entry of air was greatly diminished. A profuse bile-stained mucoid fluid could be aspirated from the trachea. Death from respiratory failure occurred twenty-six hours after birth.

Goerttler investigated the "organie unity of the musculature of the uterus" and stated that the dilatation of the cervix and lower uterine segments occurs when the arrangement of muscle fibers changes from an almost horizontal position to a vertical alignment as a result of uncoiling mechanism. He claimed that upper and lower uterine segments do not contract in different ways because of antagonistic innervation but rather because of the development of "structural changes in which contractions originally occurring in a circular direction around the uterine axis, gradually work tangentially consequent on the verticalization of the muscle units in the lower uterine segment." Muscular resistance is therefore found at the point where these essential changes take place, namely the cervix. On this basis Kreis developed at his Strasbourg Clinic what he termed the "accouchement medical" in which he used "spasmalgin," an antispasmodic which contains atropine and opiates. The antispasmodic aimed at weakening or eliminating the resistance of the active condition of contraction of the cervix and at the same time the contraction of the upper uterine segment. Ivy and Rudolph, discussing the physiology of the uterine musculature, refer to four different types of activity of the uterine musculature during labor, namely three types of contractions called auxotonic, isometric, and brachystatic, and one type of relaxation called mezystatic. The auxotonic and isometric contractions enable the uterus to exert expulsive pressure, while brachystasis is the maintenance of this tension in the shortened smooth muscle; in contrast, mezystasis is the maintenance of a lengthened status of the smooth muscle of the uterus. In the case of the uterus the upper uterine segment thickens by contracting brachystatically and the cervix dilates by relaxing mezystatically. Thus if a drug could be found that would stimulate auxotonic, isometric, and brachystatic contractions of the upper segment and at the same time allow mezystatic relaxation to occur in the lower uterine segment and cervix, this would speed up labor. Brenkhahn concluded that atropine in small doses caused a relaxation of the sphincter of the portio vaginalis of the uterus, but it was only of value in tetanic contractions. Hirsch claims that atropine causes a relaxation of the portio but has only a slight stimulating effect on the uterine body. For years it has been known that spasmodic constrictions of various muscular orifices of the human system have responded under drugs which depress the parasympathetic nervous system, atropine being used in pylorospasm, gall bladder colic and the like. Thus atropine and later syntropan whose earlier usage was restricted to spastic conditions of the gastrointestinal system was attempted in obstetrics.

Syntropan is a nonnarcotic antispasmodic, the phosphate salt of the tropic acid ester of 3-diethyl-amino-2,2-dimethyl propanol which is derived in turn from atropine by hydrolysis. Syntropan's action as a paralyzant of smooth muscle of isolated frog intestine is about twenty to fifty times weaker than atropine but its mydriatic activity is 10,000 times weaker. The drug has been used in labor by Hillis, Plinc, Stoll, Gamstatter, Hirsch and others.

At the onset of our investigation it was realized that the most important fact, and one neglected by earlier investigators, was the exact starting and end points of the first stage of labor. Rectal palpation of the cervix noting the exact amount of dilatation seemed easy and satis-

alveolus there was a clump of bacteria. Occasional alveoli contained thin, slightly refractile fibrillary-like structures which were apparently lanugo hairs. There were rare epithelial squamæ in the alveoli.

CASE 4.—The infant's condition was poor at birth and inhalations of oxygen and carbogen were frequently necessary. Respirations were feeble at times and later gasping and irregular. Cyanotic spells occurred frequently. Jaundice and a moderate amount of generalized edema developed on the second day. Death occurred on the fourth day. The hemoglobin was 86 per cent; red blood count, 4,450,000; white blood count, 8,100; nucleated red cells, 201 to 100 white cells. Histologic examination of the lungs showed large amounts of amorphous, translucent, and granular pink-staining material in the bronchi and alveoli. In this material there were rare epithelial squamæ. No lanugo hairs were seen.

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OBSERVATION ON SYNTROPAN ON THE LENGTH OF LABOR

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IN ORDER to corroborate the work of other writers, we have recently completed a series of cases in which the nonnarcotic, antispasmodic drug syntropan was used. The drug's action is similar to that of atropine. It is an inhibitor to the parasympathetic nervous system and secondarily affects the smooth muscle cell. It has been suggested as a method of materially shortening the length of labor. Abnormally prolonged labor taxes mother, infant, and physician and leads to complications which include uterine inertia, infection, and deleterious effects on both mother and infant. Unduly prolonged first stages of labor have always troubled the obstetrician and have stimulated, and many times forced, him to use various methods to overcome this difficulty; thus country practitioners were prone to use the belladonna plaster on the parturient's back. They believed that the pains became stronger and more effective, thereby shortening labor. Other physicians at times attempted more forceful means such as pituitary extract, thymophysin, etc. However, objections and disappointments were frequent and medical men have constantly looked for some harmless method to shorten materially the process of childbirth.

While it is not our purpose to discuss the subject of uterine anatomy and physiology, it may be advantageous at this point to seek out the rationale of earlier workers in attempting to use such drugs as syntropan.

was 21 years, the youngest 14 years and the oldest 34 years. Eight of these patients received a total of 100 mg. of syntropan, 6 received 200 mg., 3 received 300 mg., and one a total of 400 mg. before the first and second stages of labor were completed. The average length of the first stage was five hours and twelve minutes, while the second stage was one hour and forty-two minutes. Thirty per cent of the patients noted an increase in the severity of their pains although all were told that they were receiving an analgesic drug. In this series there were 23 multigravidas with an average age of 27 years. The maximum dosage used was 300 mg. The average length of the first stage was two hours and forty-eight minutes, the second stage lasting on an average of thirty minutes. Thirty-five per cent of the multigravidas experienced an increase in the severity of their pains.

In order to increase the possible effect of the drug, the time interval between subsequent doses was reduced to every two hours instead of three and the dosage remained the same, i.e., two tablets of 50 mg. each. Ten primigravidas were included in this group with an average age of 20 years. The first stage of labor averaged six hours and twenty minutes, an increased time of one hour and eight minutes over the previous series. The age of the 10 multigravidas averaged 27 years and the parity two. The average length of the first stage of labor was two hours and fifty-four minutes.

In the third series of patients four tablets of the drug were administered at exactly 3 cm. dilatation with two tablets being repeated every two hours. Ten primigravidas and 10 multigravidas were used. The average age of the former was 23 years, of the latter 29 years. The multigravida averaged a parity of three. Although the initial dose of the drug was thus increased 50 per cent, the first stage of labor for these primigravidas lasted on an average of eight hours and thirty minutes, thereby lengthening this stage by two hours and ten minutes instead of shortening it as many investigators have reported. The multigravidas had complete dilatations in three hours and eighteen minutes; again the first stage of labor was lengthened rather than shortened. The second stage of labor in this group averaged one hour and 23 minutes in the primigravidas, and 29 minutes in the multigravidas.

There was a total of 45 control patients. They did not receive medication but cervical dilatation was observed in a like manner. Twenty-three of the control patients were primigravidas averaging 19 years of age. The average length of their first stage was six hours and twenty-four minutes, their second stage one hour and forty-eight minutes. Twenty-two multigravidas acted as controls, their average age being twenty-seven years and their parity three. Their first stage lasted on an average of three hours and their second stage twenty-four minutes.

Summary

A total of 48 primigravidas received syntropan under various conditions as to time of administration and amount. In all instances the drug was given at a definite progress point and its effect observed from that point onward. The average duration of the first stage of labor for all primigravidas receiving the drug was six hours and eighteen minutes; the control patients averaged six hours and twenty-four minutes or a total difference of six minutes between the treated and untreated primi-

factory. Three centimeters of dilatation were chosen as the arbitrary starting point of the first stage. Thus throughout this report the first stage is said to begin at 3 cm. dilatation and ends with complete dilatation. The usual methods of determining the beginning and ending of the second and third stages were used.

Results

In our first series (Table I), 50 mg. tablets were given to unselected primigravidas and multigravidas in active labor with a cervical dilatation of 3 cm. The medication was repeated every three hours through the first and second stages. The membranes were intact in all cases and were intentionally ruptured at complete dilatation in an equal number of treated and untreated patients. Sedation, when used, consisted of morphine sulfate, gr. $\frac{1}{6}$, and scopolamine, gr. $\frac{1}{150}$. The number of cases receiving sedation was very few. This series consisted of 18 primigravidas of which 4 were colored and 14 were white. Their average age

TABLE I

	PRIMIGRAVIDAS	MULTIGRAVIDAS
<i>Control Patients</i>		
Number of patients	23	22
Average age	19	27
Parity	0	3
Drug administration	0	0
Duration first stage	6 hr. 24 min.	3 hr.
Duration second stage	1 hr. 48 min.	24 min.
Duration third stage	12 min.	11 min.
Untoward symptoms	0	0
<i>Treated Patients</i>		
<i>Series 1:</i>		
Number of patients	18	23
Average age	21	27
Parity	0	3
Drug administration	2 tab. stat, q 3 hr.	2 tab. stat, q 3 hr.
Duration first stage	5 hr. 12 min.	2 hr. 48 min.
Duration second stage	1 hr. 42 min.	30 min.
Duration third stage	6 min.	7 min.
Untoward symptoms	0	0
<i>Series 2:</i>		
Number of patients	10	10
Average age	20 years	27 years
Parity	0	2
Drug administration	2 tab. stat, q 2 hr.	2 tab. stat, q 2 hr.
Duration first stage	6 hr. 20 min.	2 hr. 54 min.
Duration second stage	2 hr. 20 min.	30 min.
Duration third stage	10 min.	9 min.
Untoward symptoms	0	0
<i>Series 3:</i>		
Number of patients	10	10
Average age	23 years	29 years
Parity	0	3
Drug administration	4 tab. stat, q 2 hr.	4 tab. stat, q 2 hr.
Duration first stage	8 hr. 30 min.	3 hr. 18 min.
Duration second stage	1 hr. 23 min.	29 min.
Duration third stage	10 min.	10 min.
Untoward symptoms	0	0

menstrual bleeding, profuse enough to require protection. These investigators examined microscopically the vaginal washings of 5 women with no gross bleeding and found blood in all. Papanicolaou³ found mild intermenstrual bleeding, too slight to be recognized by the women themselves, in 13 per cent of normal adults on the twelfth or thirteenth day of the cycle and in 24 per cent he found erythrocytes in the vaginal smear made about the time of ovulation. The flow at ovulation time is sufficiently gross to attract the attention of probably less than 5 per cent of women (Rock⁴). The cyclic occurrence of tinged leucorrhea at the midinterval may be considered a probable sign of ovulation (Mazer and Israel⁵).

The inconvenience caused by ovulation bleeding is usually negligible. Nevertheless, because of apprehension on the part of the patient, aid is frequently sought. Occasionally, however, the intracyclic bleeding may be prolonged and copious, requiring attention. It may well be that most cases of polymenorrhea may fall into this category. Endometrial polyps, submucous fibroids, cervical or uterine malignancy must be eliminated in the differential diagnosis. Curettage usually offers relief for many months but recurrences take place. Intracyclic bleeding that is sufficient enough to attract attention is abnormal. In many women the cycle is shortened to twenty-one to twenty-three days, and it appears to them that they bleed off and on. When cyclic hypermenorrhea is further complicated by profuse midmenstrual bleeding which recurs with monotonous regularity, the patient may soon be physically, as well as psychically, upset. In some patients, following right upon the prolonged menstrual flow, ovulatory bleeding may account for bleeding throughout the whole abbreviated intermenstruum.

The control of midmenstrual bleeding in a small series of 6 patients varying in age from 19 to 39 years by the use of chemically pure androgenic substances was particularly gratifying as to warrant this report. Of the patients in this series, two were sisters. Another, who had been sterile, conceived several months after menses were stabilized and therapy stopped. Two typical case reports follow:

CASE 1.—A physician's wife, 39 years of age, had a twenty-one- to twenty-three-day cycle and for the past twelve to fifteen years had been troubled with dysmenorrhea, hypermenorrhea, and midmenstrual bleeding, which was usually prolonged but only at times profuse. Various therapeutic procedures were tried with little success. Thorough curettage after the onset of a midmenstrual occurrence of bleeding revealed an early presecretory endometrium. Complete relief was obtained for a few months. Recurrence of the syndrome soon followed. The intracyclic bleeding differed from the menstrual episode in that the latter was attended by the prodromal symptoms of breast turgidity, menstrual molimina and dysmenorrhea. Thirty to 75 mg. of testosterone propionate were administered parenterally in divided doses at weekly intervals during the intermenstruum, with disappearance of the intracyclic bleeding. Therapy was continued for seven months and then stopped. Three months later there was a recurrence of the midmenstrual bleeding. When

gravidas. Forty-three multigravidas received syntropan. Their first stage of labor averaged two hours and fifty-four minutes while twenty-three control patients averaged three hours of first stage labor. It must be said that in no case did we note any unpleasant effect from receiving the drug; 30 to 35 per cent of all patients complained of an increase in the severity of their pains. Tabulation of the second and third stages of labor was incorporated simply for the completeness of the record.

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INTRACYCLIC BLEEDING

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THE periodic occurrence of bleeding during the intermenstruum varying from spotting to short bouts of hemorrhage of one or two days' duration, is occasionally encountered in apparently normal menstruating women. This bleeding occurs between the ninth and seventeenth days of the cycle and is frequently midmenstrual. This entity has been recognized by the Germans who refer to it as the "kleine Regel" (the little menstruation) and by the French who refer to it as the "règles supplémentaires" (supernumerary or false menstruation). Midmenstrual bleeding may be "a throwback" in man's phylogeny for it suggests a reversion to a primitive event in the sexual cycle which is disappearing in the process of evolution. In the rhesus monkey, intermenstrual bleeding, macroscopic or microscopic, occurs in the majority of ovulatory cycles but never in anovulatory ones.¹ Periodic interval hemorrhage has its homologue in the estrus cycle of certain lower animals. In dogs, interval bleeding occurs immediately before ovulation (proestrus) and in cows at the time of ovulation (estrus).

Midinterval bleeding is apparently related to the time of ovulation in both women and monkeys.

Hartman¹ demonstrated that intermenstrual bleeding in the macaque was an infallible sign of ovulation. In 20 per cent of 61 cases of "mittelschmerz" studied by Wharton and Henrikson² there was inter-

tration to young women of oral estrogens during the intermenstruum we have noted that some bleeding was precipitated at about the time of ovulation. This procedure may be used to indicate ovulation time in some women being treated for sterility. Zondek and others were able to reproduce the syndrome of midmenstrual bleeding by the administration of a total of 50 mg. of progesterone during the postmenstrual phase. They were able to prevent the occurrence of intracyclic progesterone induced bleeding through large doses of estrogenic hormone. The administration of androgens for the amelioration of various menstrual disorders is well established. Its action in arresting bleeding may be due to its specific myotrophic action.^{6, 7} In this series of cases although parenteral androgens proved effective, the oral administration of methyl testosterone proved more convenient and just as effective in minimizing interval bleeding without interfering with ovulation.

Summary

The ovulation syndrome of intraeyelic bleeding or of midmenstrual pain may be so annoying as to require attention. The administration of testosterone propionate parenterally in 10 to 25 mg. doses at weekly intervals alleviated the syndrome. Methyl testosterone administered orally in 5 to 10 mg. doses throughout the intermenstruum proved just as effective in minimizing and arresting midinterval bleeding or pain without interfering with ovulation.

The testosterone propionate and methyl testosterone used in this particular study were supplied as Oreton and Oreton-M, respectively, by the Schering Corporation.

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androgens (methyl testosterone) were administered orally in 10 mg. doses daily during the intermenstruum, the results were similar to that previously obtained. This therapy was continued for six months and when medication was once more discontinued there soon followed another recurrence of the bleeding though much milder in character. Re-institution of oral androgen therapy was again followed by good results. Five months later medication was again discontinued and during the past year the patient has remained free from midmenstrual bleeding except for mild spotting on the ninth day of the cycle on two occasions. The cyclic hypermenorrhea has been reduced to a normal flow, free from pain. Curettage at the onset of menses on two occasions during courses of therapy revealed excellent progestinal endometria.

CASE 2.—W. F., aged 21 years, was referred to the author with the diagnosis of menstrual migraine, dysmenorrhea, and polymenorrhea. The headaches were more or less constant though more severe when menstruating. Furthermore, though the patient menstruated every fourteen days it was apparent that the bleeding episodes alternated in character and duration. A period of profuse bleeding of about eight days' duration was attended by severe uterine cramps for the first few days. About six days after cessation of the menses another bleeding episode of three to five days' duration would occur and this was initiated by severe pain in the region of one of the ovaries. The bleeding episodes, alternating in character and duration, had been recurring with annoying regularity for several years. Parenteral doses of 10 mg. of testosterone propionate every three days were started after a midmenstrual spell and carried on throughout the next menses and the intermenstruum that followed. The next menstrual period was delayed, occurring on the thirty-third day with severe dysmenorrhea. Though midmenstrual bleeding did not occur, nevertheless, fourteen days before the onset of the ensuing period she experienced the same ovarian pain (*mittelschmerz*). With continued androgenic therapy the menses were stabilized but the dysmenorrhea persisted. Though the interval bleeding was arrested after the first month of therapy the *mittelschmerz* recurred successively for three months on the fourteenth day of the cycle. Thereafter, ovulation pain and bleeding disappeared and androgen therapy was discontinued after the fifth month. In the months that followed, the ovulation syndrome recurred but seldom. Because of the persistence of menstrual migraine, oral estrogen therapy (estriol glucuronide*) was administered throughout the intermenstruum and soon amelioration of the menstrual headaches as well as the dysmenorrhea followed. The estrogen medication did not invoke evident midmenstrual bleeding. When two courses of progesterone therapy (one, oral anhydro-hydroxy-progesterone and the other parenteral progesterone) were administered, the dysmenorrhea recurred on each occasion.

Discussion

The occurrence of midmenstrual bleeding may be explained as an atavistic feature, recalling ovulation bleeding of monkeys. The experimental observation of Hartman suggests a cause and effect relationship between the higher level of estrogen current at the time of ovulation and the intermenstrual bleeding. Frequently, following the daily adminis-

*Collip's placental estrogen, Emmenin (Ayerst, McKenna).

with a differential of 74 per cent polymorphonuclear cells with 14 non-filamented cells, 3 per cent eosinophiles, and 13 per cent lymphocytes. The urine specimen was negative.

Physical examination revealed marked tenderness in the right lower quadrant. There was, in this area, a firm palpable mass extending from the pelvis to the level of the umbilicus. The uterus was palpated just above the symphysis pubis. On bimanual examination, the cervix was soft, and the external os was closed. The uterus was the size of a sixteen weeks' gestation. The above-mentioned mass filled the right broad ligament area and seemed to fuse with the uterus. There was severe pain in the right pelvis on examination.

The differential diagnosis was: (a) a right interstitial or cornual pregnancy with possible rupture into the broad ligament; (b) torsion of the ovary.

A laparotomy was performed through a right paramedian incision extending from the symphysis pubis to the umbilicus. A pregnant uterus was located in the lower portion of the abdomen. A firm, round mass was found continuous with the right margin of the uterus. This mass had dissected between the leaves of the broad ligament. The right ovary appeared to be attached to the mass. The right Fallopian tube was identified 3 cm. below the ovary. An irregular, circular incision was made around the mass, keeping 2 to 3 cm. between the mass and the uterus. The mass was approximately 10 cm. in diameter and shelled out with difficulty. The bleeding was controlled by suturing.

The pathologist reported the specimen, grossly, to be a fibroid 9 by 7 by 6 cm., and gray in color. On section, it exhibited extensive necrosis and hemorrhage. Microscopically, the tissue was described as a new growth with a considerable amount of necrosis, degeneration, and irregularly distributed polymorphonuclear, small round, and plasma cell infiltration. The framework consisted of a fairly dense, fibrous connective tissue arranged in somewhat interlacing bundles (Fig. 1). There were many areas in which the cells were quite anaplastic with the tendency to be spindle shaped, although in many areas, they were polyhedral and round. The spindle-shaped cells were arranged in bundles that ran in different directions. The polyhedral and round cells were arranged in irregularly shaped masses, most of which were quite small, interspersed amid the connective tissue and tumor tissue cells (Fig. 2). The microscopic diagnosis was degenerating fibroblastic sarcoma.

The postoperative course was uneventful, and the patient was discharged on October 21.

A routine examination, January, 1942, showed a blood pressure of 114/62, fetal heart rate 144 per minute, and a cephalic presentation without engagement.

The patient was re-admitted to the hospital on Feb. 28, 1942, near term. Confronted with the possibility of rupture of the uterus during active labor, an elective cesarean section was performed. The abdomen was opened through a right paramedian incision closely approximating the rectus scar. There were no adhesions about the uterus, intestines, or the abdominal wall. The fetus apparently aspirated fluid before extraction and required tracheal suction as well as artificial respiration. The placenta was delivered without difficulty. Bleeding from the uterine mucosa was quite profuse. The thickness of the uterine musculature could not be determined. The uterus was closed in three layers. The right ovary and Fallopian tube were closely adherent to the wall of

DEGENERATING FIBROBLASTIC SARCOMA OF THE UTERUS COMPLICATING A PREGNANCY

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SARCOMA is a comparatively rare neoplasm of the uterus; sarcoma complicating pregnancy has been recorded only five times in the past seventy years.

In 1885, Bernardy¹ reported a gestation in a sarcomatous uterus, simulating an ectopic pregnancy, which aborted during the fifth month. Death was due to plenrisy with effusion and ascites. Autopsy revealed an enlarged uterus with the endometrium entirely replaced by "adenosarcoma."

A fibrosarcoma complicating a three months' gestation was reported by Eastman¹ in 1897. A panhysterectomy was performed.

Nisot,¹ in 1922, reported a pedunculated, sarcomatous, degenerated fibroid complicating a four months' pregnancy; this was treated by a subtotal hysterectomy.

On the nineteenth day of the puerperium, Hesseltine,² in 1930, diagnosed sarcoma of the endometrium. Panhysterectomy and x-ray were employed.

Der Brueke,¹ in 1933, reported a myosarcoma complicating a four months' gestation. The pedicle was tied off and the fibroid mass was enucleated. Five months after operation, she went into labor and delivered normally.

Case Report

The patient, V. R., aged 35 years, presented herself for examination and prenatal care on Sept. 20, 1941. The history revealed that the onset of her last menstrual period was on June 9, 1941. The expected date of confinement was March 16, 1942. There were three previous pregnancies; of these, one was a miscarriage that occurred between her first and third full-term pregnancies. The full-term pregnancies terminated in twelve-hour labors, normal deliveries, and no complications. Catamenia: onset at thirteen; twenty-eight-day cycle; 4 to 8 days' duration. There was no history of pain, pathologic bleeding, or leucorrhea. The patient had had measles, mumps, pertussis, and scarlet fever. Tonsillectomy and adenoidectomy, appendectomy, and cholecystectomy had also been performed. The physical examination revealed no pathology.

The patient was seen again on October 6, at which time she complained of severe abdominal cramps. The pain was described by the patient "as simulating that of an abortion." There was no vaginal bleeding. She was given morphine sulfate, $\frac{1}{4}$ grain, and was instructed to stay in bed. This treatment did not alleviate her symptoms, so she was hospitalized on Oct. 12, 1941.

On admission to the hospital, her temperature, pulse, and respirations were recorded as 98.2° F., 76, and 18, respectively. Her blood picture showed the red blood cells to be 4,120,000, white blood cells were 13,300

the uterus. Both mother and infant left the operating room in apparently good condition.

The postoperative course was uneventful, and mother and infant were discharged on the tenth post-partum day.

On the first of May, eight weeks post partum, an examination showed the abdominal scar to be contracting; the breasts empty; the uterus well involuted and movable; and the adnexa normal. To date, there has been no evidence of recurrence.

The sarcomatous tumors of the uterus may be grouped as those arising in or from: (a) the muscle or connective tissue; (b) myomas; (c) the mucous membrane; and (d) the blood supply.⁴ The most frequent type is that arising from myomas. The tumor may be macroscopic or microscopic, the corpus uteri being involved more frequently than the cervix uteri.

Grossly, the tumor resembles raw pork; the sarcomatous area situated, most often, centrally with extension peripherally. Necrotic changes, if present, are brainlike, pultaceous, broken-down areas with or without ragged cavity formation. Hemorrhage may or may not be present. The endosarcoma is a polypoid structure, and cervical sarcoma is grapelike in structure.

Microscopically, sarcoma is of the spindle, round, giant, or mixed cell type. Metastasis may occur by: (1) direct continuity; (2) blood stream to the lungs and liver; and (3) lymphatics.

Novak^{3, 4} reports 59 instances of sarcoma, none of which complicated pregnancy, and 1,263 cases of carcinoma over a twenty-five-year period. Sarcoma comprises but 4.5 per cent of all uterine malignancies. Vogt⁵ reports the ratio of sarcomatous to carcinomatous degeneration to be between 1:30 and 1:40. The literature shows the incidence of sarcomatous degeneration of myomas to be 0.76 per cent (Table I).

Sarcoma of the uterus is usually a disease of middle life, more especially of the climacteric. The symptoms are not distinct, and the diagnosis is made by microscope. The following signs and symptoms, none characteristic of sarcoma, may occur:^{4, 12}

A. Early: (1) Abnormal bleeding, such as menstrual excess and intermenstrual flow. (2) Abnormal discharge, thin and watery becoming serosanguineous. (3) Rapid increase in the size of the tumor.

B. Late: (1) Pain, (2) anemia, (3) cachexia, and (4) weakness.

Myomas influence pregnancy in that they may interfere with the equable development of the uterus and frequently cause abnormal pres-

TABLE I. THE INCIDENCE OF SARCOMATOUS DEGENERATION IN MYOMAS

	CASES OF MYOMAS	CASES WITH SARCOMATOUS DEGENERATION	INCIDENCE (%)
Kimbrough ⁷	3,388	26	0.76
Kimbrough ⁷	91,310	701	0.76
Review of the literature			
Imhauser ^{8, 11}	208	11	5.30
Evans ⁹	4,000	72	1.8
Kelly and Cullen ^{9, 11}	1,400	17	1.2
Novak ^{3, 4}	6,981	Sarcoma secondary to myomas	0.56
		39	
Vogt ⁵	30	8	0.6
Vogt ⁵	72,116	300	0.41
Review of the literature			



Fig. 1.

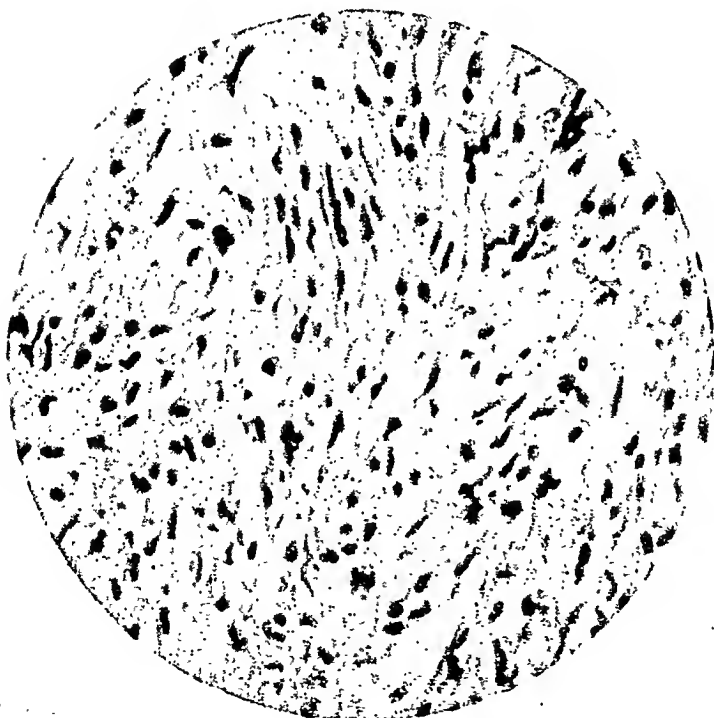


Fig. 2.

3. The incidence of a sarcomatous degeneration of a myoma complicating a pregnancy is rare, being 0.0044 per cent.
4. The operative removal of the degenerating myoma gives a better prognosis for a full-term pregnancy.
5. The most prominent and only consistent symptom of sarcomatous degeneration of a myoma complicating pregnancy is pain.
6. The diagnosis of sarcoma in the greatest percentage of cases depends upon microscopic examination.

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Addendum

Since the writing of this paper, another case of sarcoma of the uterus complicating a pregnancy has been encountered.

The patient, aged 22 years, gravida i, was admitted to the hospital on Aug. 25, 1942, with the complaint of vaginal bleeding. Her last menstrual period began March 11, 1942. The expectant date of confinement was Dec. 18, 1942. There was no history of bleeding, cramps, or other pathologic conditions until Aug. 24, 1942, at which time she began to have persistent lower abdominal cramps. Profuse vaginal bleeding occurred a few hours later; and early the morning of the twenty-fifth, she was delivered of a five months' fetus. Inability to deliver the placenta resulted in the hospitalization of the patient.

On admission, the temperature, pulse, and respirations were recorded as 100.6° F., 100, and 20, respectively. Urinalysis was negative.

Physical examination revealed no pathologic conditions of head, nose, throat, lungs, or heart. There was no spasm, rigidity, or tenderness in the abdomen. No scars or herniations were present. The uterus was palpated just above the symphysis pubis. There was moderate vaginal bleeding.

The temperature, spiking in character, rose gradually to 101.4° F. on Aug. 27, 1942. A fibroid polyp, the size of a baseball, was removed from the uterine cavity.

The pathologist reported the specimen, grossly, as an encapsulated purple tumor that measured 8 by 7 by 6 cm. and which exhibited areas of degeneration on section. Microscopically, the tissue was described as a new growth made up of interlacing bundles of various-sized spindle cells. Many of them were small, closely packed, and had hyperchromatic nuclei and little cytoplasm. A few mitotic figures were present. Necrosis and free hemorrhage were described as existing throughout the tumor mass. The microscopic diagnosis was spindle cell sarcoma. It was the pathologist's recommendation that panhysterectomy be performed.

The placenta was passed the following day, Aug. 28, 1942. The temperature dropped to normal where it remained until the patient was discharged on Sept. 3, 1942.

entations, premature labors and deliveries, and infection. They offer a definite operative risk. Any of these, singly or collectively, may result in fatality of either mother or infant or both. The incidence, however, of myomas complicating pregnancy is less than 1 per cent (Table II).

Pregnancy causes an enlargement of myomas which may become detrimental, in that incarceration and dangerous compression of the pelvic organs may occur. There is an increased vascularity of the tumor, and the growth may undergo any of the various types of degeneration.

The symptoms of a myoma complicating pregnancy may be:^{10, 13}

- a. Pain, at times quite marked.
- b. Hemorrhage, simulating a threatened abortion.
- c. Constipation, dysuria, and cachexia, if the tumor mass is large and abdominal overdistention occurs.

After a review of the literature and the present case study, it is noted that the outstanding feature of the preoperative history and physical examination is its resemblance to that of the ordinary fibroid in pregnancy, the exception being cases of far-advanced sarcoma. One may postulate that any fibroid tumor which enlarges rapidly, irrespective of size, and is the source of pain and embarrassment to the patient should be removed. If the capsule has not been involved, simple enucleation is the procedure of choice and the pregnancy is allowed to go to term, even in the presence of early sarcomatous degeneration.

The present policy of conservatism in the management of fibromyoma in the presence of the menace of sarcoma should not be altered nor should the menace prevent the use of radium and roentgen ray because sarcoma is radiosensitive.¹⁴

TABLE II. THE INCIDENCE OF PREGNANCY COMPLICATED BY MYOMAS

	NUMBER OF CASES OF PREGNANCY	NUMBER COMPLICATED BY MYOMAS	INCIDENCE (%)
R. E. Campbell ¹⁰	32,870	142	0.43
Pierson ¹⁰	30,856	250	0.80
Pinard ¹⁰	13,915	84	0.60
Total	77,641	476	0.61

In cases where the capsule is involved and extension is in the early stages, treatment consists of panhysterectomy and irradiation. However, due to the lack of diagnostic symptoms and to the fact that microscopic malignancy does not necessarily imply clinical malignancy, few cases can be so treated with resultant cures.

Wagner,⁶ Patel and Eparvier,¹ Hardouin and Broult¹ have shown that sarcomas, although dormant and unsuspected, do, during pregnancy, suddenly become activated, grow rapidly, and may prove fatal.

The prognosis in sarcomatous degeneration of a myoma is three times more favorable than in primary sarcoma. The criteria for primary sarcoma are:⁷ (1) absence of other myomas; (2) absence of gross and histologic evidence of a pre-existing myoma at the site of the sarcoma.

Summary

1. Sarcoma of the uterus is a rare tumor comprising but 4.5 per cent of uterine malignancies.

2. Sarcomatous degeneration of myomas occurs in 0.5 to 2 per cent of the cases.

The abdomen was obese with a well-healed lower midline scar. No distention was present. The lower abdomen was tender to direct and indirect pressure. A symmetrical mass rose from the pelvis to a point one finger below the umbilicus. No fetal heart was heard. Contractions were not palpable.

The vaginal outlet presented moderate relaxation of both anterior and posterior walls. A greenish yellow discharge was present. The cervix was effaced and dilated 4 to 5 cm. A soft fetal head with overriding sutures presented at the external os. The urine was negative. The white blood cells numbered 11,350, with 87 per cent polymorphonuclear leucocytes. The red blood cells numbered 3.5 million, and there were 11 Gm. of hemoglobin. Culture of the cervix revealed *Staphylococcus albus*, diphtheroids, and nonhemolytic streptococcus. The latter was predominant. A roentgenogram of the abdomen demonstrated a 6 months' fetus with overriding of the cranial bones.

A diagnosis of inevitable septic abortion with dead fetus was made. Seven minims of posterior pituitary extract were given in divided doses to initiate labor. A course of sulfathiazole was begun.

After eight hours, the cervix dilated to 6 or 7 cm., though no contractions were palpable. The temperature rose to 103° F., and the pulse to 120. A tenaculum was applied to the fetal scalp, and by gentle traction, a living female fetus was delivered. The child measured 32 cm. from crown to heel and weighed 896 Gm. The fetus lived for thirty-three hours.

The placenta did not separate. Blood loss was about 500 c.c. The patient was taken to the operating room for a manual removal of the placenta. During the procedure, the "uterine" wall felt extremely thin, and it contained many huge sinuses. Four large pieces of placenta were removed. The remaining fragments were left attached for fear of manually rupturing the viscus, and a tight pack was used to control the bleeding which was estimated to be an additional 800 c.c. The patient was transfused with 800 c.c. of plasma and 1,000 c.c. of citrated blood, during and after this procedure. Two hours later, the blood pressure fell abruptly from 120/70 to 80/60. The "uterus" had increased in size. The pack was removed and brisk vaginal bleeding followed. A laparotomy was decided upon because of inability to control the hemorrhage and fear of rupturing the "uterus" by further manipulation. Transfusions of plasma and citrated blood were started.

On opening the peritoneal cavity, a thin-walled sac was found occupying the central portion of the pelvis extending up to the pelvic brim. Its surface was hobnailed and had a mottled purplish blue color. Numerous large branching veins crossed its surface. The lateral superior surfaces were covered by the ascending and descending colon, respectively. The cecum was easily displaced laterally, exposing the right tube, ovary, and round ligament. On the left side, the sigmoid was adherent to the sac wall. This was freed, exposing the left ovary. The left tube was identified as the large thin walled sac (Fig. 1). The wall was ruptured in the attempt to elevate the sac. The exposed cavity was lined with fibrous tissue, coagulated blood, placental fragments, and many blood sinuses. Its wall was 2 to 3 mm. thick, and communicated with the vagina. The infundibulopelvic ligaments were clamped, cut, and ligated. The sac was excised below the level of the upper part of the cervical canal. The edges were approximated with interrupted chromic sutures. The abdomen was closed with through-and-through

The patient was readmitted to the hospital on Sept. 21, 1942. The interval history was noncontributory. X-ray studies of the bones in the lower abdomen, pelvis, and thighs revealed no evidence of invasion by neoplastic metastases. Chest x-ray also revealed the absence of pathologic conditions. Blood count showed 4,200,000 red cells, white cells 3,250 with a differential of 51 per cent polymorphonuclear cells with 10 nonfilamented cells, 3 per cent eosinophilic cells, 1 per cent basophilic cells, 3 per cent monocytic cells, and 42 per cent lymphocytic cells. The hemoglobin was recorded as 14 Gm., or 84 per cent.

On Sept. 24, 1942, a panhysterectomy was performed. No evidence of metastases was observed in the pelvic organs at the time of operation. The pathologist reported no evidence of sarcoma in the uterus, Fallopian tubes, or ovaries.

The first four postoperative days were characterized by temperature and pulse elevation up to 102.2° F. and 120, respectively. Cystitis and gas pains were the only complications. The patient was discharged in apparently good condition on Oct. 4, 1942.

Follow-up examination, two months after operation, revealed no evidence of recurrence or metastases.

VAGINAL DELIVERY OF A SIX MONTHS' LIVING CHILD FOUR YEARS AFTER SUPRAVAGINAL HYSTERECTOMY

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THIS case is reported because it represents an unusual sequela of supravaginal hysterectomy.

L. D., a 44-year-old Italian woman, was admitted to the gynecologic service of the Long Island College Division of the Kings County Hospital on March 1, 1942, complaining of lower abdominal pain and a yellowish vaginal discharge for the past three days.

The past history was not significant except as it related to the present illness.

Obstetric History.—The patient had been married for the past thirteen years. She was a gravida viii, and a para iv. One child was stillborn. There were two miscarriages in the fourth month, the last in 1936. This was followed by curettage.

Her menses began at the age of 13 and occurred regularly every thirty days, with a 6- or 7-day flow. Since 1936, the periods had become more profuse and prolonged. Following six weeks of bleeding, a supravaginal hysterectomy was performed in 1938 at the Queens General Hospital. This was followed by amenorrhea until four days before admission.

Present Illness.—The patient was well until four days before entering the hospital. Since then, she had had vaginal bleeding and colicky pain in the lower abdomen. The bleeding ceased after one day and was followed by a profuse yellow vaginal discharge. Both the pain and the discharge persisted until admission.

Physical examination revealed an acutely ill woman, complaining of abdominal pains. The temperature was 101.4° F., pulse 112, and blood pressure 130/78.

many ghost villi were observed. These villi extended down to the superficial portion of the muscular coat and were surrounded by an exudate of polymorphonuclear leucocytes and round cells (Fig. 3). Vascularity was pronounced and diffuse areas of hemorrhage common.

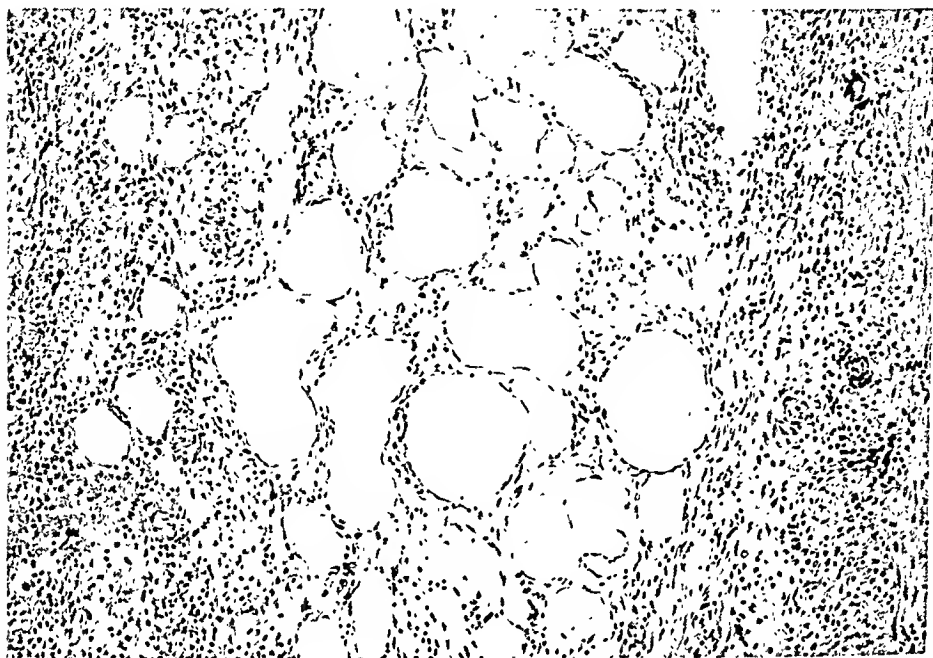


Fig. 2.—Area of fat in subperitoneal region. Dense cellular infiltration and hemorrhage in surrounding areas.

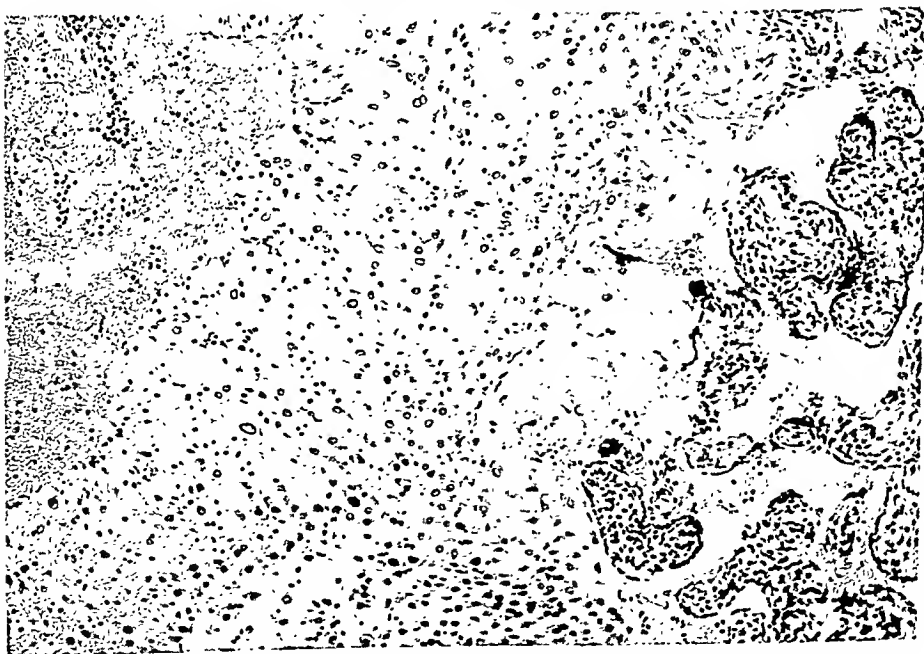


Fig. 3.—Well-defined villi attached to a fibrinoid layer. Beneath is a layer of decidual cells. A large venous sinus traverses the lower border.

black silk sutures. The patient was transfused with an additional 650 c.c. of pooled plasma and 3,400 c.c. of citrated blood before, during, and after this procedure.

The patient rallied postoperatively. Gross hematuria was noted on the first postoperative day and persisted throughout the entire course. Cystoscopy was performed on the eighth day. The bladder mucosa was not visualized due to the opacity of bloody urine. A small fragment of tissue was removed from the bladder wall for pathologic examination. Only clotted blood was seen in the microscopic section. Excretion urography showed the dye to be present in the lower portion of both ureters. The urine output was ample at all times and on the fifth day,

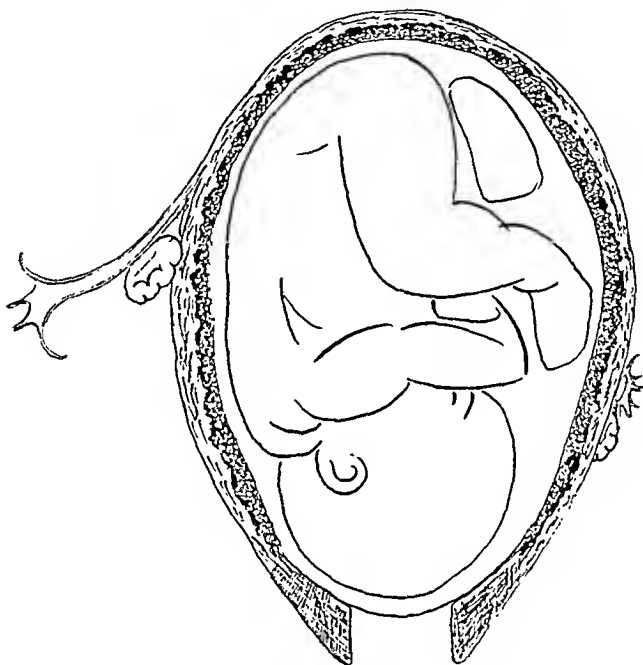


Fig. 1.—Frontal view of gestational sac in left tube, showing continuity with cervical canal.

2,500 c.c. were excreted. The blood urea determination on the second postoperative day was 76 mg. per 100 c.c. of blood, on the fourth day, 64, and on the eighth day 53. At no time was there an elevation of the blood creatinine. The abdominal wound healed with slight superficial separation of the edges. The patient's temperature ranged between 99° F. and 101° F., while the pulse varied from 100 to 120. Three additional blood transfusions were given on the fifth, tenth, and fifteenth postoperative days, totaling 1,600 c.c. Signs of a bronchopneumonia developed on the fourteenth postoperative day. This was confirmed by a roentgenogram of the chest. The patient died March 18, the sixteenth day postoperatively. Permission for autopsy was refused.

Pathologic Report.—Microscopic Examination: Sections through the wall of the specimen revealed the tissue to consist of smooth muscle whose component cells were large, spindle in shape and contained abundant cytoplasm with a large pale blue elongated nucleus. The muscle bundles showed no interlacing or interdecussation and were arranged in more or less parallel sheets. Beneath the subperitoneal coat, islands of fat were frequently seen (Fig. 2). The interior of the sac was covered with blood and fibrin, presenting varying stages of organization, in which

TABLE I. TABULATION OF PREVIOUSLY REPORTED CASES

AUTHOR	PREVIOUS OPERATION	INTERVAL, BEFORE PREG- NANCY	SITE OF PREGNANCY	OUTCOME
Keller	Supravaginal hysterectomy	2 years	Extrauterine	Death due to intra-abdominal hemorrhage
Wendeler	Vaginal hysterectomy	6 years	Tube	Gestational sac curetted. Recovery
Jacques	Subtotal hysterectomy, bilateral salpingectomy, right oophorectomy	4 years	Cul-de-sac posterior surface of bladder	Posterior colpotomy, recovery
Liepmann	Supravaginal hysterectomy	2 years	Tube	Death due to intra-abdominal hemorrhage
Bower	Supravaginal hysterectomy, right salpingo-oophorectomy	3 years	Tube	Laparotomy. Living 7 mo. fetus. Recovery
Connors and others	Supravaginal hysterectomy	4 years	Tube	Vaginal delivery of a living 896 Gm. fetus. Partial manual removal of placenta. Laparotomy with removal of the gestational sac. Death due to bronchopneumonia sixteen days postoperatively

infundibulopelvic ligaments were attached to the cervical stump. Conditions favorable to the establishment of a fistulous tract were therefore fulfilled. Unfortunately, the previous operative report was not at hand when the patient was admitted to the Kings County Hospital.

Treatment of the patient as an inevitable abortion was based on the presentation of the fetal vertex at the external os of the cervix. We were unable to find any similar case, where, in the absence of the uterus, the cervical canal was dilated sufficiently to effect vaginal delivery. However, contractions of the hypertrophied tubal musculature evidently produced dilatation of the cervix. The cause of the hematuria postoperatively is unexplained, despite investigation of the urinary tract. Incomplete penetration of the bladder wall by the placental villi is offered as a possible explanation for the hematuria.

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Diagnosis.—Pregnancy within the tube, associated with an acute inflammatory reaction.

Discussion

Pregnancy following hysterectomy is rare, though instances of tubal and abdominal pregnancies have been recorded in the literature. A review of the literature failed to reveal a single instance of an authenticated case of vaginal delivery of a living child from a tubal gestation following supravaginal hysterectomy.

Five cases of pregnancy have been reported, occurring in women from whom the uterus had been removed. In 1872, Keller¹ quoted Koeberle as having known a patient who died from a ruptured extrauterine pregnancy, two years after he had performed a supravaginal hysterectomy. Wendeler² reported a tubal gestation, six years after vaginal hysterectomy. He successfully curetted this gestational sac through a tubovaginal fistula which offered easy access through the vagina. Complete recovery occurred. Jacques³ described a case in which a posterior colpotomy enabled him to deliver a 9 cm. fetus from a gestational sac on the posterior aspect of the bladder, four years after subtotal hysterectomy with bilateral salpingectomy and right oophorectomy. Liepmann⁴ emphasized the rarity of such pregnancies. He reported a death due to intraabdominal hemorrhage from a ruptured tubal pregnancy two years after supravaginal hysterectomy. Bower⁵ described a successful laparotomy with delivery of a seven months' living child, almost three years after supravaginal hysterectomy and right salpingo-oophorectomy. Grigg's patient⁶ had a supravaginal hysterectomy performed on her one year before she was delivered at home of a full-term pregnancy by a midwife. Neither Grigg nor any other physician had seen the patient during pregnancy or delivery. Both Jaboulay⁷ and McMillan^{8, 9} describe laparotomies for cases of pregnancy following hysterectomies. However, in both instances menstruation occurred after the initial operative procedure. This suggests that part of the fundus had been left. In addition, their operative notes describe what was interpreted by them as uterine tissue.

The occurrence of pregnancy following hysterectomy must depend upon a fistulous tract between the vagina and the ovary. It is common practice for gynecologic surgeons to attach the remaining adnexa to the cervical stump after extirpation of the uterus. This places the proximal end of the tube adjacent to the cervical canal. The failure of many sterilization operations by mere ligation of the tubes is proof enough that continuity of the tubes may be re-established. In like manner recanalization of a tube, ligated during a hysterectomy, can easily occur. After tubal ligation, fortunately for those women who are not castrated at operation, contiguity with a patent cervical canal is not often established.

An analysis of all the reports cited showed that a fistulous tract was established between the vagina and the ovary. In one such case of pregnancy,³ both tubes and one ovary were removed; an opening was made from the posterior surface of the cervix to the vagina to permit drainage and the remaining ovary was placed adjacent to the cervix. In the others, the proximal ends of the tubes were sutured to the cervical stump. In our case, a review of the operative report from the Queens General Hospital reveals that a supravaginal hysterectomy was done for endometrial hyperplasia and myometrial fibrosis. The round ligaments and

A series of 30 menopausal women, all of whom were private patients, were treated with ethinyl estradiol. There was one woman under thirty years of age, 10 between thirty and forty years, 18 between forty and fifty, and 1 over fifty. Fourteen patients were postoperative, 2 post-radium, and 13 in natural menopause. The usual symptoms of the menopause syndrome were present. Hot or cold flushes, nervousness, and emotional instability, myalgia, insomnia, etc., were the characteristic symptoms. Most of these patients had been under active treatment previously. They had received alpha-estradiol, alpha-estradiol benzoate, stilbestrol or other preparations. These women emphasize the usual recurrence of the symptom complex with cessation of any form of estrogenic therapy. They further offer a means of establishing some clinical comparison of the value of various preparations used.

The dosage of ethinyl estradiol was maintained at 0.05 mg. daily. This amount was less than that prescribed by Salmon and others.⁵ These observers required from 0.45 to 0.15 mg. daily dosage of ethinyl estradiol to produce satisfactory clinical relief of symptoms and produce objective evidence of estrogen activity in vaginal smears. Approximately 25 per cent of their patients developed undesirable gastric symptoms which required cessation of therapy. The nausea, vomiting, malaise, and abdominal pain subsided promptly on discontinuation of therapy. We established 0.05 mg. ethinyl estradiol as a sufficient dose with which to anticipate therapeutic response after having noted "estrin-withdrawal" bleeding after administering a total of 0.85 mg. of ethinyl estradiol in a period of seventeen days. With this dosage (0.05 mg. daily), 28 of 30 patients, 93 per cent, tolerated this estrogen well. One patient was severely nauseated and one experienced a sense of "bloating" and gastric distress requiring cessation of medication.

The response to ethinyl estradiol was uniformly satisfactory with administration of 0.05 mg. daily. Nineteen patients (63 per cent) exhibited an excellent response with complete relief of all symptoms and a fine emotional lift. Nine (30 per cent) responded well. Flushes, etc., were under good control, and the patient was grateful for the medication. Thus 28 of the 30 women could be said to have a satisfactory response to 0.05 mg. of ethinyl estradiol daily. One patient showed no reaction to the medication. Flushes were as severe as before. One patient noted slight if any improvement.

The question arises as to the relative efficacy of ethinyl estradiol as compared with the synthetic estrogen-like drug stilbestrol. Our experiences with stilbestrol have been eminently satisfactory. We have not experienced the oft-noted toxic side-actions, probably because of our adherence to minimal dosage. However, even though stilbestrol has proved satisfactory in controlling the menopause syndrome and relieving other evidence of estrogen deficiency, it was noted quite frequently that the patient who obtains a similar result with natural estrogens experiences a

A CLINICAL TRIAL OF ETHINYL ESTRADIOL

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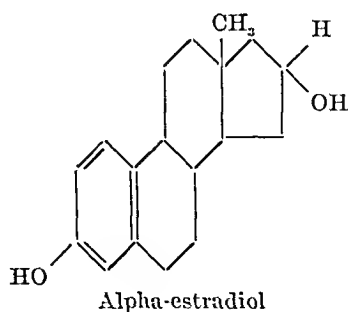
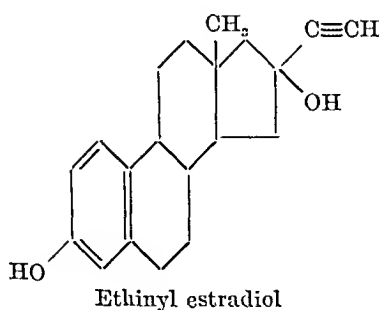
THE use of estrogenic preparations in various disorders of the female is becoming established on a rational basis. Recognition of the need for this type of therapy always has been recognized. The obstacles, such as inconvenience of administration of hypodermic injections, inconstancy of standardization, undesirable side action, and expense, have made estrogen therapy difficult.

The isolation of crystalline estrone^{1, 2} from human pregnancy urine established a basis for further investigation. Chemical analysis revealed estrone to be keto-hydroxy-estrin. Schwenk and Hildebrandt³ reduced the Keto group to a secondary alcohol creating dihydroxy-estrin which is known as estradiol.

Estradiol is most likely the hormone actually produced by the ovarian follicle.⁴ It is the most potent of the natural estrogens. Referring back to the obstacles which stand in the way of more free use of estrogens, estradiol is the most satisfactory ovarian hormone available for oral administration.

In the very recent past, ethinyl estradiol has been offered as an extremely potent estrogen.

This preparation is closely related in its chemical structure to alpha-estradiol.



The new compound therefore differs from alpha-estradiol only in having the hydrogen in position 17 of the latter compound replaced by the ethinyl group, H—C≡C—. This change in the structure, however, confers a remarkable increase in effectiveness by oral administration.

In a previous paper⁶ we have compared the potency of various estrogens in the production of estrin-withdrawal bleeding. In this patient ethinyl estradiol was considered to be at least fifty times, and possibly more nearly seventy times, as active as alpha-estradiol.

DEMEROL (S-140) AND SCOPOLAMINE IN LABOR*

A Preliminary Report

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DURING a study of the clinical effectiveness of some of the newer analgesic drugs, our attention was drawn to the report of Battermann on demerol.¹ This compound is 1-methyl-4-phenylpiperidine-4-carbonic acid ethyl ester. The drug possesses both atropine and morphine-like properties embodying a spasmolytic action on smooth muscle of the gut, uterus, and bronchial tree with a slight sedative and marked analgesic effect.² Demerol may be administered orally or parenterally, and, in therapeutic doses has very little effect on the respiration. This latter point prompted us to use the drug combined with scopolamine in a series of patients during labor.

Preliminary trial indicated that oral administration was ineffective in the parturient patient and the following plan of medication was therefore followed. When the patient began to mind her pains, regardless of the state of dilatation of the cervix, she received 100 mg. of demerol intramuscularly and scopolamine gr. 1/100 subcutaneously followed by scopolamine gr. 1/200 in one hour. This was sufficient to maintain the multiparous patient throughout the balance of her labor, while primiparas required additional medication in the form of scopolamine gr. 1/200 every one to five hours.

This preliminary report is concerned with 112 consecutive cases of patients treated with demerol and scopolamine. The type of delivery, condition of the baby, anesthesia, and maternal amnesia are shown in Table I.

All patients remembering more than a few pains after receiving the initial medication or those who, without questioning, would tell of being moved to the delivery room or of receiving anesthesia were thought to have poor amnesia. Our criteria for the determination of the amnesic state have been as rigid as possible in order to cut down the error from subjective impression. There was no correlation between the terminal anesthetic and the activity of the newborn infant. Any baby needing excessive stimulation, catheter suction, or oxygen was judged slow.

In Table II will be found the averages for the length of labor and the time of medication before delivery. The possibility of prolonging labor

*The demerol used in this study was furnished through the courtesy of the Alba Pharmaceutical Co., Inc.

peculiar "lift" or sense of well-being that is difficult to explain but which is nevertheless frequently definite.

It is difficult to estimate the relative efficacy of various estrogens in a wholly clinical study such as this. Twelve of the patients who had previously taken from 0.25 to 1.0 mg. of stilbestrol daily approximately were equally benefited by 0.05 mg. of ethinyl estradiol. Five patients who had previously been kept in balance with 0.5 mg. of alpha-estradiol orally were equally benefited by 0.05 mg. of ethinyl estradiol.

Summary

1. A series of 30 postoperative, postradiation and natural menopause patients were treated with ethinyl estradiol.

2. Ethinyl estradiol is the most active oral estrogenic hormone we have used to date.

3. Daily dosage of 0.05 mg. of ethinyl estradiol was found to be therapeutically satisfactory in 93 per cent of the patients.

4. Ethinyl estradiol was well tolerated in 93 per cent of the cases.

The ethinyl estradiol (Estinyl) used is a product of the Schering Corporation.

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Lehman, Edwin, and Boys, Floyd: *Clinical Use of Heparin in the Peritoneum for the Prevention of Adhesions*, *Arch. Surg.* 43: 933, 1941.

From experimental studies on dogs, continued for more than two years, the authors definitely concluded that intraperitoneal application of heparin diminishes the number of reformed adhesions after their division. This fact they ascribe to the reduced coagulability of the serous exudate which is the first response to peritoneal traumatization. It prevents the formation of fibrin, the essential element in organization.

The writers detail clinical data of 14 patients in whom old adhesions were severed during a repeated laparotomy. After completion of operation and careful hemostasis through a stab wound through the abdominal wall near the greatest number of adhesions, 10,000 units of heparin in 300 c.c. of physiologic salt solution is permitted to run by gravity through a previously introduced catheter into the closed abdominal cavity. There was one death "due to bad selection of the case and inadequate hospital observation."

Hemorrhage will remain a potential hazard and the method should not be applied if oozing is difficult to control or granulation tissue is present. Postoperative observation must be careful and continuous.

OBSERVATIONS ON DEMEROL AS AN OBSTETRIC ANALGESIC

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Material

In 150 white women delivered vaginally during 1941 and 1942, the synthetic compound "demerol" (1-methyl-4-phenyl piperidine-4 carbonic acid ethyl ester; Alba) was used during labor. Two-thirds of the cases were ward and the rest were private patients. One hundred twenty-four were primiparous and twenty-six were multiparous women. In 70 cases, demerol was used alone and in 80 cases in combination with other drugs. Caudal anesthesia with 35 c.c. of 1 per cent novocain was used in 75 deliveries, nitrous oxide with oxygen and ether in 74 deliveries, and no anesthesia in 1 delivery. The drug was administered both orally and parenterally, though a majority of patients received intramuscular injections of the hydrochloride because of greater uniformity and rapidity of effect when so given.

Effect on Length of Labor

Patients were admitted in every stage of labor up to full dilatation and thus medication could not invariably follow a consistent plan. Analysis of these cases show certain significant facts.

Primipara.—Regardless of age, degree of cervical dilatation with the initial dose, character of labor, presentation or position, 54 primiparas received demerol alone. The highest dosage used was 650 mg. and the lowest was 100 mg. The average dosage was 294 mg. The average time elapsing between the initial dose, usually 100 or 200 mg., and the end of labor, was five hours and four minutes. The average time elapsing between the final dose, invariably 100 mg., and the end of labor, was two hours and forty-two minutes. The average total length of labor was eleven hours and eighteen minutes.

If we exclude 4 breech presentations, 9 persistent occiput posterior and transverse positions, 2 cases of uterine inertia, and 11 cases in which the initial dose was given with the cervix more than 4 cm. dilated, 28 primiparas received demerol alone, and in this group average findings are most significant in regard to the effect of this drug on length of labor. In these selected cases, the highest dosage used was 500 mg. and the lowest 100 mg. The average total dosage was 285 mg. The average time elapsing between the initial dose and the end of labor was four hours and forty-two minutes. The average time elapsing between the final dose and the end of labor was two hours and twenty-two minutes. The average total length of labor was nine hours and six minutes.

TABLE I

Total number of cases	112
<i>Type of Delivery:</i>	
Primiparous normal delivery	18
Primiparous low forceps delivery	34
Primiparous breech delivery	3
Multiparous normal delivery	48
Multiparous low forceps delivery	7
Multiparous breech delivery	2
<i>Condition of Babies:</i>	
Active	96
Slow	16
<i>Anesthesia:</i>	
Ether	73
Spinal	21
Pentothal	11
None	7
<i>Amnesia:</i>	
Good	95
Poor	17

TABLE II

<i>Average Length of Labor:</i>	
Primiparas	12 hr. 2 min.
Multiparas	8 hr. 46 min.
<i>Average Time of Medication Before Delivery:</i>	
Primiparas	4 hr. 28 min.
Multiparas	2 hr. 14 min.

by the use of demerol and scopolamine is not apparent in this series. Eight primiparous patients required pituitrin stimulation in the second stage of labor for secondary uterine inertia.

The condition of patients receiving this medication was, in general, favorable. The incidence of vomiting or other undesirable side effects was no greater than when other types of medication were used. Occasionally patients complained of dizziness, but the attending euphoria mentioned in earlier reports¹ was not present. The majority of patients were conscious enough to be cooperative and restlessness was kept at a minimum by the infrequent administration of scopolamine.

We feel that demerol and scopolamine bear promise of being safe and effective means of medicating full-term patients during labor, while the absence of serious respiratory depression in the newborn makes this type of analgesia particularly suitable in obstetrics.

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spasmodic effect acting upon the cervix,* or may simply result because the patient bears down more vigorously when the pain threshold is raised.† A personal communication from Dr. J. M. Hiebert (Department of Clinical Research, Alba) states that in the intact and active dog uterus, uterine tone and contractions are slightly increased under demerol administration. Our patients showed no evidence of uterine hypertonicity.

Doses of 100 mg. of demerol even when given at onset with the cervix not effaced, will not stop labor or diminish the effectiveness of mild contractions.

Analgesia and Amnesia

For several years the drugs usually employed at this hospital for obstetric analgesia and amnesia have been seconal and heroin; these were given to one-half to two-thirds of the patients conducted through labor during the months when demerol was investigated, and served as a background for our observations on the action of this drug.

In no case where demerol was used alone was amnesia, as distinct from analgesia, obtained in any degree.

Analgesia.—The difficulty of translating "analgesia" into quantitative terms is apparent. For purposes of this paper we arbitrarily decided upon three terms for three grades of analgesia. Grading was done on the basis of observation of each woman in labor, and after an interview twenty-four hours after delivery. "Excellent" analgesia occurred when the patient stated that her labor was not painful at all. Analgesia was considered "good" when the patient was quiet and controlled during labor and upon questioning affirmed that her pains were not more than she could stand and provided she did not recall her labor as an extraordinarily painful experience twenty-four hours after delivery. "Slight" analgesia was a state less satisfactory.

Of the 70 patients receiving demerol alone (Cases 1 to 54, and 125 to 140), analgesia was good in 51, slight in 19; no patient ever reported "excellent" analgesia in the absence of amnesia. Thus, 72 per cent of this group obtained adequate analgesia without amnesia, according to our criteria. It will be recalled that more than one-half of these cases were ward patients.

Amnesia.—Again, three terms for 3 grades of amnesia have been arbitrarily applied. "Excellent" amnesia was a state in which the patient, on questioning twenty-four hours after delivery, remembered nothing from shortly after the administration of seconal until some time after return to her room or ward following delivery. "Good" amnesia was a state in which the patient could vaguely recall isolated events during labor or delivery; with "good" amnesia memory of pain was absent or minimal. "Slight" amnesia referred to a state less satisfactory than this, and especially when memory was weighted with recollection of pain.

Of the 72 patients receiving demerol and seconal, amnesia was excellent in 8, good in 36, slight in 27, and entirely lacking in 1; i.e., 61 per cent of patients obtained satisfactory amnesia according to our criteria. These results are statistically poor. This was because our be-

*Climenko: Proc. Am. Physiol. Soc., March, 1942.

†Batterman: Proc. Am. Soc. Pharmacol. & Exper. Therap., March, 1942.

In addition to the 54 primiparas receiving demerol alone, the drug was used in combination with seconal in another group of 63 primiparous women regardless of age, degree of cervical dilatation with initial dose, character of labor, presentation, or position. The average dosage of demerol was 240 mg. and of seconal (Lilly) 5.9 gr. The average total length of labor was eleven hours and forty-eight minutes, substantially the same as in the unselected series of 54 primiparas who received demerol alone. That the 62 primiparas receiving demerol and seconal averaged thirty minutes longer in labor than the 54 primiparas who received demerol alone, is no more than a sampling error.

TABLE I. SUMMARY OF ALL CASES

		AVERAGE DOSE	AVERAGE LENGTH OF LABOR HR.: MIN.		AVERAGE LENGTH AFTER INITIAL DOSE HR.: MIN.		AVERAGE LENGTH AFTER FINAL DOSE HR.: MIN.	
Patients receiving demerol alone								
Primipara	54	D.294 mg.	11	18	5	4	2	42
Multipara	16	D.262 mg.	9	4	3	40	1	46
Patients receiving demerol and seconal								
Primipara	62	D.240 mg. Sec. 5 9 gr.	11	48	5	33	2	9
Multipara	10	D.240 mg. Sec. 3. 9 gr.	6	6	1	58	1	3
Patients receiving demerol and various drugs								
Primipara	8	—	21	52	—	—	—	—
Multipara	0							

In addition to the 116 cases discussed above, 8 primiparas, as a result of therapeutic vagaries, received demerol in combination with seconal, heroin, and paraldehyde. This group includes several extended labors in which the patient was given a period of rest by means of fairly heavy sedation during the first stage; hence, the average length of labor is twenty-one hours and fifty-two minutes. Except that such combinations showed no evidence of incompatibility, these cases provide no further information.

Multipara.—Included in the experiment were 26 multiparas, 16 receiving demerol alone, 10 receiving demerol and seconal. Twenty-one were para i, 3 were para ii, 1 was para iv, and 1 was para viii. In the 16 cases receiving demerol alone the average length of labor was nine hours and four minutes, and in the 10 cases receiving demerol and seconal the average length of labor was six hours and six minutes. Again, the small number of cases doubtless accounts for the apparent shortening of labor when seconal is given.

We believe it likely that in analgesia of multiparas demerol alone may prove to be particularly suitable, since often the institution of a major amnesic regime to carry such cases through an easy labor seems scarcely warranted.

With experience limited to only 150 cases, conclusion as to the effect on length of labor must be tentative, but we feel that shortening of labor occurs when demerol is given. This may be the result of the drug's

is that reported by Benthin in Germany "Analgesia in Obstetrics Through Dolantin."^{*} This report states that the third stage of labor seems to be shortened, and likewise that mild atony of the uterus is a feature, in women delivered under dolantin (demerol) analgesia. We cannot confirm these observations.

The high incidence of forceps procedures in our series is not related to the analgesic drugs used, since here elective outlet forceps deliveries are usual with primiparas.

Effect on the Baby

We believe that the addition of nitrous oxide or ether to the fetal environment just before birth significantly accentuates the depressant effect on the baby of whatever hypnotics or sedatives the mother may have received during labor, even when great care is taken to avoid anoxemia. Therefore, the use of caudal anesthesia at the termination of labor, we believe, contributed to an accurate evaluation of demerol's effect upon the baby.

Of the 70 women, 54 primiparas and 16 multiparas, in whom demerol was used alone, 40 were delivered under caudal anesthesia, 29 under nitrous oxide and ether, and 1 with no anesthesia. Of these 70 babies born, with or without cutaneous stimulation, active respiratory movements were initiated in 66 within sixty seconds of the time the cord was cut. The cord was sometimes left intact for one or two minutes after delivery when the baby was small, or following difficult forceps procedures. In this group, 3 babies (4.3 per cent) breathed only after insufflation. Because of the presence of apnea it was decided to insufflate the lungs with pure oxygen immediately, although we believe all three would have lived without this expedient. After artificial oxygenation lasting only one or two minutes, all three progressed normally.

No babies delivered of mothers receiving demerol alone showed any persistent cyanosis, evidence of narcosis, or otherwise merited the term "sleepy baby" where this is meant to describe drug effects.

One baby in this group died shortly after birth. The mother, a para iv, progressed from 2 cm. dilatation to the end of labor in fifty-six minutes. After uneventful spontaneous delivery, the baby presented an appearance suggesting intracranial damage, but fetal atelectasis was the autopsy diagnosis. We believe intrapartum medication received by the mother did not contribute to the cause of death.

Of the 80 women, 70 primiparas and 10 multiparas, in whom demerol was used in combination with other drugs, 35 were delivered under caudal anesthesia and 45 under nitrous oxide and ether. Of 80 babies born, 69 breathed spontaneously. Ten babies (12 per cent) breathed only after insufflation.

In the presence of apnea at birth, it is our practice to allow ordinary methods of cutaneous stimulation only a brief trial, usually not more than one minute, before resorting to insufflation to relieve anoxemia. It cannot be denied that the addition of barbiturates to demerol analgesia has a slight to moderate depressant effect on the baby, but in the dosages recommended it is rarely of disturbing degree. Fetal narcosis

^{*}Deutsche med. Wchnschr., No. 25, pp. 760, 1940.

lief that demerol would potentiate the hypnotic action of barbiturates (see Climenko's work cited above) led us to give a number of women during labor only $1\frac{1}{2}$ to 3 gr. of seconal. While an occasional case would obtain satisfactory amnesia with this low hypnotic dosage (see Cases 62 and 66), particularly after fairly large amounts of demerol had been given, less than $4\frac{1}{2}$ gr. of seconal were uncertain. Demerol does potentize the action of seconal enough to reduce significantly the amount of this hypnotic necessary to obtain amnesia in the labor patient. With proper utilization of seconal in a patient adequately prepared with demerol, amnesia can be obtained consistently with smaller doses of the barbiturate than can be used successfully alone, and with other advantages not possessed by unmodified hypnotic regimes.

The 8 women who received demerol in combination with seconal, heroin, and paraldehyde, usually obtained excellent or good amnesia.

Other Maternal Effects

With large doses of demerol (300 to 500 mg.) a moderate sedative effect was noticed and women would frequently sleep between pains. This was never so pronounced that the patient would not awaken when spoken to in an ordinary conversational tone.

No excitement, disorientation, or irrationality because of the drug was noticed in patients under demerol alone.

Complaint of dizziness and light-headedness was occasionally noted in our series but was not prominent.

Complaint of thirst and dryness of the mouth was frequent. With patients delivered under inhalation anesthesia, this depressed secretory activity in the nasopharynx had an obvious advantage.

In Batterman's 800 cases cited above, drawn from other fields of medicine, he reports that nausea and vomiting occur in approximately 5 per cent of patients receiving demerol. This small percentage would be hard to identify in observations made upon obstetric patients, since in many vomiting is an expected feature. We have noticed no increase in the number of women in labor that vomit since we began this investigation.

Investigators in other branches of medicine have also reported an euphoric effect in patients under demerol medication. If connotation of excitement is excluded from the term euphoria, a similar effect may be affirmed for the parturient. Nervous and apprehensive young primiparas often appear to be emotionally fortified after moderate doses of this drug, and thereafter to meet the stress of labor with greater equanimity. In part, this psychological effect may be consequent to elevation of the pain threshold, but in addition a certain primary influence on emotional state is probable. Briefly, they seem braver.

No post-partum depression, confusion or "hangover" as a result of demerol medication occurred.

No effect on the third stage was seen. Bleeding was not increased. The only previous work on the use of demerol in obstetrics known to us

patients difficult to control and requiring restraint, but these were definitely exceptional and would doubtless have presented a nursing problem under any circumstances.

Summary and Conclusions

1. Demerol in doses of 100 to 400 mg. noticeably shortens labor in primiparas.
2. The analgesic effect of this drug in the dosage recommended is sufficient to carry many normal primiparas through an entire labor with satisfactory subjective result.
3. No effect on the baby by demerol in this dosage was noted.
4. Demerol alone in doses up to 650 mg. has no amnesic effect.
5. Demerol combines well with seconal when amnesia is sought, and noticeably potentizes the action of this hypnotic.
6. The use of demerol as recommended permits an elastic type of obstetric care during labor. Conduct of each case may be individualized in accord with the character and rapidity of labor: the decision to institute amnesic therapy, with its additional nursing responsibility and possible risk to mother and baby, may be made relatively late, depending upon the reaction of each patient to the stress of labor.

The constructive criticism and advice of Dr. John G. Murray, Jr., together with the additional material provided by the use of many of his private patients in the experiment, contributed materially to this paper.

TORSION OF THE UTERINE ADNEXA IN CHILDHOOD

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THE twisting of ovarian tumors, especially cysts, is of fairly common occurrence. The symptoms and signs accompanying this condition are so well appreciated that the diagnosis is frequently made before operation. The relative infrequency of ovarian tumors in childhood probably accounts for the rarity with which twisted ovarian tumors or cysts are encountered. According to Smith and Butler, only 25 instances of torsion of ovarian tumors before puberty were reported in the literature in twenty years.

Torsion of the normal uterine adnexa is rarely seen. It is said that the incidence is greater than supposed because many cases are not reported. This is hardly a valid argument, however, because it is true of all conditions and the reported cases should give a fair idea of the frequency with which it is met. In 1921 only 14 cases of torsion of the normal adnexa could be found and of these, only 4 were under twelve years of age. Shute, in 1932, said that 35 cases of torsion of the normal ovary had been reported. In the ensuing nine years several cases have

was not a major factor in the apnea presented by these babies. All breathed and progressed normally after a brief period of artificial oxygenation.

In this group also one baby died shortly after birth. The mother, a normal gravida i, underwent amniorhexis in the second stage of labor. At delivery velamentous insertion of the cord with rupture of an umbilical vessel was found. The baby was exsanguinated and transfusion was unavailing.

We suggest the following program for the use of demerol in obstetrics. (1) As soon as regular contractions are definitely established, even though at fifteen- to twenty-minute intervals and with the cervix not completely effaced and not dilated, 100 mg. of demerol are given intramuscularly. (2) One hour later, with presumably some progress made in effacement and dilatation, a second 100 mg. is given. If labor has been rapid, or if the cervix was thin and 2 to 3 cm. dilated at the first dose, the second 100 mg. may be given one-half hour after the first. (3) One hour later, or when the cervix reaches 4 cm. dilatation, if progress has been rapid, a third 100 mg. is given.

By the time this stage is reached the obstetrician will have decided whether or not to add amnesia to his analgesic therapy. With many a normal primiparas, 300 mg. of demerol, given by the time the cervix reached 4 cm. dilatation, will enable her to continue through labor up to the second stage without undue exhaustion from the pain and psychic distress of labor. As before noted, normal primiparous labors under demerol administration tend to be short. If it is decided to conduct labor under demerol alone, a fourth 100 mg. dose may be given by the time the cervix reaches 5 cm. dilatation. In any event, we believe it advantageous to complete the total demerol dosage early in labor. The action of this drug is sustained and its perceptible effect is maintained for six hours after any single dose. Four hundred milligrams of demerol given by the time the cervix is 5 cm. dilated, or 4 cm. if it gives evidence of being a rapid labor, we believe to be about optimum. We feel that there is little to be gained by exceeding this dosage and at present cannot recommend that further doses be given later in labor until five to six hours have elapsed. In most cases the baby will be born before that time.

In those localities where insurance of amnesia is a prerequisite to successful obstetric practice, it will usually be found possible to carry the patient under demerol alone up to 4 or even 5 cm. dilatation before she "needs" amnesia. Concurrently with administration of the third or fourth 100 mg. dose of demerol at 4 or 5 cm. dilatation, $4\frac{1}{2}$ gr. of seconal are given by mouth. One-half to one hour later an additional $1\frac{1}{2}$ gr. of seconal is given. In the great majority of cases this dosage and sequence will insure adequate amnesia for the ensuing four to six hours, and short quiet labors are the rule in our experience. Under demerol and seconal, amnesic therapy, we have seen 2 or 3 excited

eralized abdominal tenderness and the patient cried because of pain. Muscle spasm was absent. Later, when the child was exhausted, she slept during the examination. The external genitals were normal. Rectal examination was not entirely satisfactory.

Urinalysis showed an absence of albumin and sugar, a specific gravity of 1.025, acid reaction, and 2 leucocytes per high power field. The leucocytes in the blood numbered 20,100 and the differential count was: polymorphonuclears 72 per cent; lymphocytes, 27 per cent; basophiles, 1 per cent. Roentgenologic examination of the chest was negative.

Our impression was that the patient presented the symptoms and signs of mesenteric lymphadenitis but the diagnosis of acute appendicitis could not be entirely discarded. After considerable deliberation and discussion, operation was decided upon.

Under nitrous oxide, oxygen and ether anesthesia a small McBurney incision was made. As the peritoneum was opened there was an escape of a large quantity of clear fluid followed by a smaller amount of slightly bloody fluid. The appendix was long but only mildly injected. There were many fairly large glands in the mesentery of the small bowel. Low in the abdominal cavity there was a firm mass several centimeters in diameter. It was barely possible to bring this small mass into view, and it was seen to be nearly gangrenous in appearance. It seemed advisable to have greater exposure so, after removal of the appendix and closure of the small McBurney incision, a small left rectus incision was made and the rectus muscle retracted laterally. The mass was found to be the left tube and ovary which were twisted 180 degrees in a counter-clockwise direction. The tube and ovary were removed and the pedicle doubly ligated. The uterus and right adnexa were small and normal in appearance. The wound was closed in layers.

Pathologic Report.—The specimen consisted of the left tube, the left ovary, and the appendix. The tube and ovary formed a mass which was black in color and which measured 3 by $3\frac{1}{2}$ by 2 cm. The ovary alone measured $2\frac{1}{2}$ by 2 cm. and the tube was $4\frac{1}{2}$ cm. in length. The infundibulopelvic ligament and the mesosalpinx were edematous, thickened, and twisted. The cut section of the ovary was dull and black. There were two small cysts, each measuring 5 mm. in diameter. On microscopic examination, it was seen that the cortex was fairly intact; the remainder of the normal structure was obliterated by hemorrhagic infarction. The tube also contained blood, the result of infarction. The appendix, which measured 7 cm. by 5 mm., was slightly injected.

The patient made an uneventful convalescence and was dismissed from the hospital on May 4, the sixth postoperative day. The wounds healed by primary intention.

This is the youngest patient reported with torsion of the uterine adnexa. It is interesting that mesenteric lymphadenitis was associated and was the preoperative diagnosis. If the possibility of the condition is kept in mind it may be possible to make the correct diagnosis before operation, especially if the torsion occurs on the left side. In this case both the ovary and the tube had become twisted, but we believe that the torsion was initiated by the ovary.

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been described, mostly in the foreign literature, but from the figures available it is obvious that torsion of the normal uterine adnexa is not common. As an intern at the Johns Hopkins Hospital, one of us (H. B. N.) had experience with torsion of the normal uterine adnexa in an adult. In childhood the condition is extremely rare.

Graves is of the opinion that torsion of an ovary is very rare and that the Fallopian tube is more frequently the victim of volvulus. He stated that the ovary may be twisted off completely and, becoming embedded in adhesions, remain in the abdomen as a parasitic body. On the other hand, Smith and Butler said that there is some question whether a normal tube can undergo torsion, but it seems proved that a normal ovary may become twisted. In the 14 cases reviewed by Auvray, the tube alone was involved in 5, the tube and ovary in 8, and the tube, ovary and broad ligament were twisted in 1.

The consensus of opinion is that the right side is involved more commonly than the left. It has been mentioned that surgeons are more eager to operate when right-sided pain is present, and for that reason lesions on the left side may be overlooked. As etiologic factors abnormal length and mobility of the tube or of the mesosalpinx, spiral course of the tube, and slight enlargement and prolapse of the ovary have been suggested. Blood pressure changes in the tubal mesentery which produce venous stasis are stated to cause torsion.

Pain is the predominant symptom produced by torsion of the adnexa. It is usually colicky in character, it may be very severe, and it may come on gradually. Leucocytosis is moderate. No one claims to have made the diagnosis preoperatively. Appendicitis is the diagnosis most commonly made, but in the adult the symptoms may simulate those of tubal pregnancy. The condition could hardly be definitely distinguished from mesenteric lymphadenitis or from a twisted hydatis of Morgagni.

Report of Case

A girl, aged three years and seven months, was first seen on April 29, 1942. She had always been well except for an episode of pyelonephritis from which she recovered completely. She had been breast fed and had received cod-liver oil and orange juice intermittently.

The mother stated that in August, 1941, the child began to complain occasionally of abdominal pain. Although there were three or four attacks each week, no attack was thought to be serious enough to necessitate calling a doctor. There was no vomiting and no diarrhea. The patient ate well and the bowels moved satisfactorily.

Just before supper on April 28 the patient began to complain of crampy pain low in the abdomen. It was said that she pointed to the left side to show the point of pain. She was very restless that night, did not sleep well, and was frequently doubled up in pain. At 4 a.m. April 29 she awakened and was given a laxative tablet. Soon thereafter she vomited, and later she vomited again several times. The patient did not want to walk and she held herself in a stooped position when on her feet.

Physical examination revealed a slender girl. The skin was clear and the glands were not enlarged. The tonsils were moderately large and the crypts prominent, but there was no acute inflammation. The lungs were clear and the heart was negative. The abdomen was flat and symmetrical. When the patient was first seen by one of us there was gen-

diameter. The surrounding epithelium of the vulva was normal. No evidence of extension, either locally or at a distance, was apparent. Because of the proximity to the meatus and the vascularity of the growth, it was destroyed by means of electrocoagulation rather than by excision. The pathologic report was as follows: "Numerous glandular and tubular formations composed of columnar epithelium. Many of the glands did not have a distinct basement membrane. The nuclei

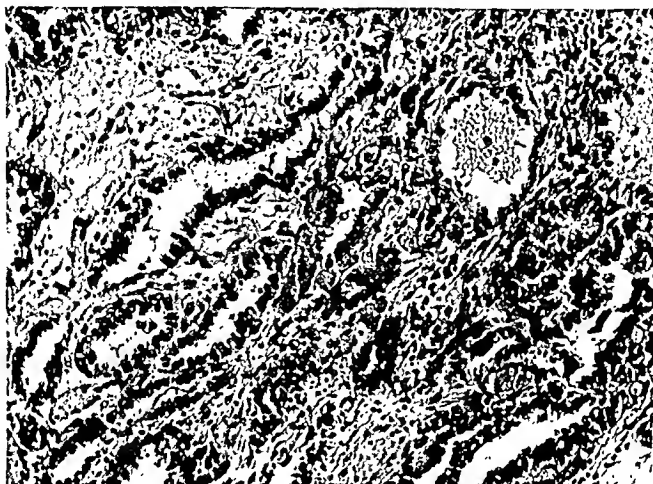


Fig. 1.—Low power. Extruded tissue from hidradenoma vulvae.

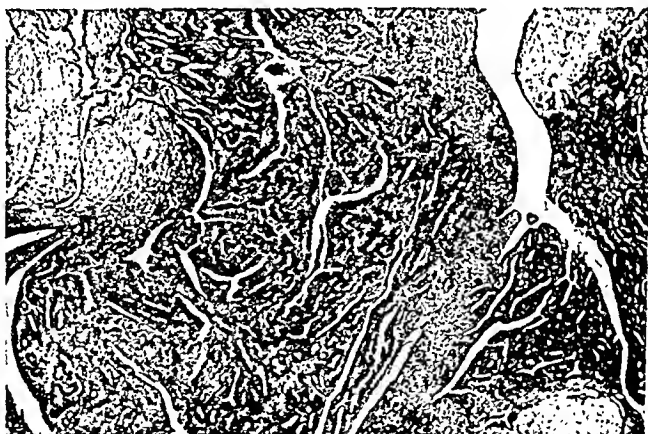


Fig. 2.—High power of characteristic two-layer epithelium, high columnar cells set on a basal layer of poorly defined cuboidal cells.

were round. In places the glands were multi-layered. There was an occasional mitotic figure and hyperchromatic nucleus present with a relatively small amount of edematous interstitial tissue in which were numerous engorged veins, few polymorphonuclear leucocytes, plasma cells, and lymphocytes. There was considerable erythrocytic extravasation.

CASE 2.—A woman, aged 50 years, had a small mass on the labium near Bartholin's gland. This was excised by her physician, the removal being quite simple. Under the microscope the same glandular picture was seen as had been observed in the first case.

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HYDRADENOMA VULVAE*

W. C. DANFORTH, M.D., EVANSTON, ILL.

SQUAMOUS cell carcinoma of the vulva is not uncommon. Surgical literature contains considerable material on the subject and treatment has been fairly well standardized. Adenocarcinoma is far less common and benign tumors of the vulva are not frequently seen. One of the more frequent of the benign tumors is fibroma of which Leonard¹ found 6 in 23,000 gynecologic cases at the Johns Hopkins Clinic. In a period of thirty-three years at the Mayo Clinic Lovelady, McDonald, and Waugh² found 34 cases of benign tumor. Of these, 16 were fibromas, 7 lipomas, 5 hemangiomas, 2 leiomyomas, 1 ganglioneuroma, and 1 lymphangioma. During this time 32 adenocarcinomas were found in the same clinic.

A number of neoplasms of glandular type have been described. Among these have been growths arising from aberrant breast tissue which may be found in the vulva, tumors arising from the remains of the Wolffian duct, and a growth, first described by Pick³ in 1904, and which he termed hydradenoma. These tumors apparently arise from the vulvar sweat glands. Sweat glands vary in different parts of the body. Over the greater part of the body the sweat glands secrete a watery fluid. In certain limited areas, as the axilla, perianal region, to a more limited extent in the areola of the breast, are found sweat glands in which the secretory activity varies from that exhibited by the usual gland in that a portion of the cellular cytoplasm is excreted. These are known as apocrine glands. Such glands are found among the lower animals where they are said to have a part in sex activity.

It is from these apocrine glands that adenocarcinoma of the vulva arises. Adenocarcinoma of the vulva is a tumor of far less malignancy than the squamous cell type of vulvar cancer. Growth is slower and metastasis later and less extensive. From these glands arise also the nonmalignant glandular vulvar growth, the hydradenoma. This is a rare tumor. According to Novak⁴ about 40 had been reported up to 1940. It is probable that if all hydradenomas were recognized many more would be reported. As has been the case with some of the more recently recognized tumors of the ovary, familiarity increases the number which are found. Our own experience with this growth is limited to two cases.

CASE 1.—A woman of 77 years. On the anterior left part of the vulva, not far from the meatus, was seen an irregularly round red mass. This was soft in consistency and not tender and about 3 cm. in

*Presented at a meeting of the Chicago Gynecological Society, March 20, 1942.

papillomatous tumor tissue. Fig. 2 is a high-power photomicrograph of the epithelium covering several papilli. This two-layer type of epithelium, high columnar placed on poorly defined cuboidal cells, is said to be characteristic of hidradenomas, the benign sweat-gland tumors of the vulva.



Fig. 1.

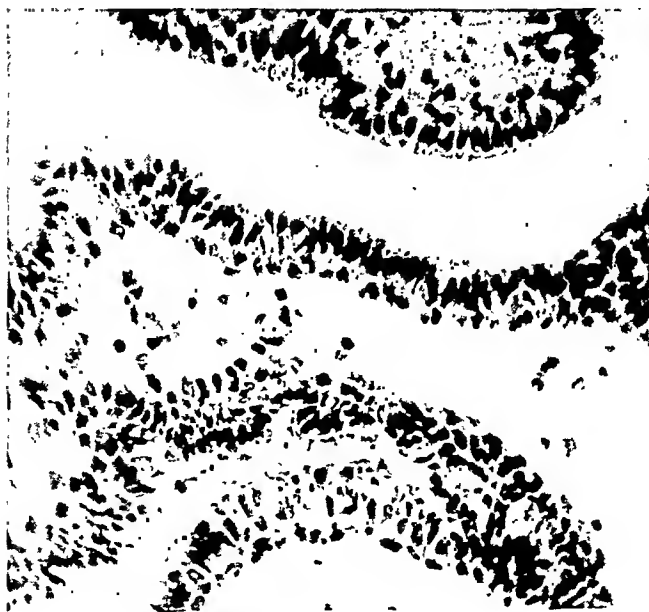


Fig. 2.

DR. A. F. LASH.—Hidradenoma vulvae has been considered an uncommon gynecologic condition, but is probably more common than indicated by the reports in the literature. According to Lynch only 22 cases have been described, the first

Clinically these tumors are important because of the ease with which they may be confused with carcinoma. When the patient, reported as Case 1, was first seen it was thought that the lesion was probably malignant, the true character of the tumor being recognized only after the examination of a specimen obtained by biopsy. Treatment is not difficult, complete excision being usually entirely satisfactory. If excision presents any difficulties destruction of the mass may be accomplished by means of electrocoagulation. It is important that the true nature of the tumor be recognized, for, should the surgeon consider that it is malignant, an unnecessarily radical operation may be done. As the growth is quite painless, many very small ones may be considered as moles by the women who have them and they do not come to the attention of the surgeon.

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Discussion

DR. GEORGE H. GARDNER.—Hidradenoma vulvae is the term applied to those benign adenomatous tumors of the vulva which in all probability arise from sweat glands. Some observers, in fact, have been able to demonstrate a direct continuity between normal sweat glands, or their excretory ducts, and hidradenomas. These tumors are rare. Most of them have been found in the fifth decade of life. They may occur either in the greater or the lesser labia, or in the sulci between the labia, but they are usually found in the labia majora where sweat glands are more abundant. They are tumors of the skin; most of them are small, as a rule not more than a centimeter or two in diameter. They may occur either as semi-solid grayish white tumors just beneath the epidermis; or, if the thinned-out covering epidermis ruptures, they become pedunculated red, fungus-like, papillomas which are attached to the skin.

Microscopically they are polycystic; they are richly adenomatous and almost invariably there are papillary outgrowths into cyst cavities; consequently from a histopathologic standpoint they are often papillary cystadenomas. Characteristically some of the alveoli are lined by two layers of epithelium, the inner layer being high columnar cells with nucleus toward the base and the peripheral layer is composed of indistinct large cuboidal cells. In other alveoli the epithelium may be a single layer of high columnar cells, or several layers of cuboidal cells.

These tumors are benign. They rarely cause symptoms unless the skin over them becomes ulcerated. If they rupture, the extruding papillomatous tumor may bleed when traumatized. It is possible that hidradenomas undergo malignant change, but this has never been proved. They may be mistaken for cancer both because of their gross appearance and their odd microscopic structure.

They may be confused with metastatic adenocarcinoma as in a case under my observation. The patient was a 45-year-old nullipara with Stage III adenocarcinoma of the cervix. Besides the tumor of the cervix there was found a nodule in the upper portion of the left greater labium, a pearly-gray firm tumor of the skin, approximately 8 mm. in diameter. It proved to be cystic and ruptured during removal; a tiny mulberry-like mass of white tumor tissue escaped from its cavity. At first this was thought to be a skin metastasis, but in reality, it was a typical hidradenoma vulvae. Fig. 1 is a low-power photomicrograph of the extruded

REPEATED SECONDARY RUPTURE OF THE PREGNANT UTERUS

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REPEATED secondary rupture of the pregnant uterus is a rarity. In the standard American textbooks of obstetrics it is mentioned only by Williams in an indirect reference to a Frenchman, Mikhine¹ who reported a series of thirteen cases in 1902. When, in addition to its rarity, it occurs under the watchful care of a group of competent obstetricians in spite of all precautions, it warrants inclusion in the literature.

Separation of the musculature of the uterus without previous incision or separation is termed primary rupture and is usually due to trauma of delivery or attempted delivery, severe labor especially in the presence of cephalopelvic disproportion, and miscellaneous and idiopathic causes. Separation of the musculature of the uterus following previous incision (usually cesarean section or myomectomy) is termed secondary rupture. The type of section predisposing to this accident is predominantly the classical rather than the low flap; Aeken² states that 7 of his 8 cases of secondary rupture followed previous classical incisions while only one followed the low flap type of section. DeLec³ states in his 1940 *Yearbook* that only 5 ruptures have been reported in the past twenty-five years following the low flap type. Secondary rupture itself is rare, Aeken² reported that his 8 cases occurred in a series of 25,935 deliveries, or an incidence of 0.03 per cent. Occurrence of repeated secondary rupture is apparently so rare that it is unmentioned in standard textbooks; a survey of recent literature disclosed no individual case reports.

Case Report

This 38-year-old, para ii, gravida iii, first presented herself at the prenatal clinic on Sept. 4, 1940. Her last menstrual period had occurred on April 27, 1940, and her expected date of confinement was Feb. 3, 1941. Her first child had been delivered by classical section in a local hospital on Feb. 9, 1932; the hospital reported that she had been admitted in her eighth month because of vaginal bleeding, a tentative diagnosis of placenta previa had been made and a classical cesarean section done. A living female child weighing 5 pounds 13 ounces was delivered and survived. Several large blood clots in the uterine cavity and partial detachment of a normally implanted placenta established the diagnosis of abruptio placentae. The patient made a normal recovery without morbidity and was discharged on her eleventh postoperative day.

The following report of her second pregnancy was received from Dr. H. J. Thomson of the County Maternity Hospital, Bellshill, Glasgow, Scotland, where it terminated in March, 1933:

"This patient was admitted here on March 13, 1933, from our prenatal clinic for cesarean section on account of previous history of cesarean section in New York for placenta previa. The operation was arranged to

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by Braun in 1892. The lesion was more completely studied by Pick in 1904, who described the development of true adenocarcinoma in 3 of the 30 cases he investigated (Teacher). Ruge, Gross, Outerbridge and Schwarz also reported cases of sweat gland adenoma. Pick described it as a slowly growing small tumor arising from the sweat glands of the vulva. Microscopically he found tubular acini lined by a double layer of nonciliated epithelium and surrounded by a capsule of elastic tissue. He traced a sudoriferous duct from the tumor to the skin surface in his cases. Cystic changes were frequent and intracystic papillary proliferations were often found. These tumors may be single or multiple, smooth or ulcerated, appearing over the mons veneris, labia majora or minora. Although these tumors are usually benign occasionally they may be malignant and, therefore, these tumors, like all tumors of the vulvae, especially in older women, warrant careful scrutiny and investigation. The following is the report of a case:

The patient, D. Z., a white woman, 50 years of age, was admitted to the Michael Reese Hospital because of menorrhagia, abdominal cramps, relative incontinence and urgency of indefinite duration. Her past history contained nothing of significance. She still menstruated every twenty-eight days as described above. She had been married for twenty-nine years and had had two full-term pregnancies with uneventful terminations and two miscarriages. The vulvar nodule did not annoy her.

Examination disclosed a small, ulcerated, hard nodule (4 mm. in diameter) on the left labium majus which was freely movable without any associated inguinal adenopathy. There was also noted a scarred perineum, from an old third-degree laceration; a large, hard, nodular cervix; a hard enlarged corpus the size of a six weeks' pregnancy; and normal adnexa.

On Dec. 21, 1936, the vulvar tumor was removed and a vaginal hysterectomy, anterior colporrhaphy and perineorrhaphy were performed. The pathologic report was adenomyosis and myofibroma of the uterus, cervical abscess and an ulcerated, pedunculated sweat gland adenoma. The microscopic section of the sweat gland adenoma showed tubular acini lined with nonciliated columnar epithelium and surrounded by connective tissue stroma. The patient made an uneventful recovery and after five years there has not been any recurrence.

It is of interest to note that aberrant breast tissue may form an adenofibroma as described by Barteky and Purvess and Hadley. These histologic pictures resemble those of sweat gland adenoma which fact is understandable since their embryologic origin is the same, i.e., breast and sweat gland.

Gambino, A.: The Action of a Sulfonamide Derivative Upon the Genital Apparatus of the Guinea Pig, *Rassegna d'ostet. e ginec.* 49: 163, 1940.

The author reviews the literature which deals with the effect of sulfonamide derivatives upon the blenorrbagias and spermatogenesis. Five groups of guinea pigs, a total of 16 individual animals, were given daily doses of red-prontosil, intramuscularly, over a period of twenty days. In two groups the dosage was 0.025 Gm. per kg. of body weight while the 2 remaining groups were given massive doses, a total average of 1.87 Gm., for a three-day period. The animals were sacrificed and their genital tracts studied.

The histologic studies of the male animals revealed large numbers of inactive sperm in the epididymus; the germinal elements of the testicles showed regressive changes while the epididymal walls appeared thin and weakened. In one group receiving red-prontosil for forty days there were found but scant numbers of sperm in the seminiferous tubules and more marked tissue changes. The tissues of the females and control animals revealed minimal and variable results.

CLARE E. FOLSOME.

A spinal injection of 8 mg. of pontocaine and 60 mg. of novocaine diluted with 3 c.c. of cerebrospinal fluid, was given in the third lumbar interspace at 5 A.M. in conjunction with 50 mg. of ephedrine sulfate intramuscularly.

A midline incision extending from the pubis to the level of the umbilicus was made down to the fascia and hemostasis obtained. The fascia was incised and the muscles separated, exposing the peritoneal fat which was infiltrated with blood in the lower half of the incised area. The tissues were edematous. No definite peritoneum was recognized, and there was difficulty in obtaining entrance to the peritoneal cavity until it was realized that the adhesions from the previous incision had bound the uterus to the abdominal wall. Entrance was then easily made to the right of the midline. In the bloody area, palpation revealed the infant's head separated only by filmy adhesions from the examining finger. An incision was made in the upper portion of the exposed uterus and extended downward with bandage scissors. On reaching the bloody area in the lower uterine segment, however, the scissors encountered no resistance, and it was then realized that there had been a silent rupture of the lower third of the old scar. Up to the time of operation there had been no gross bleeding nor extrusion of the uterine contents, probably because of the adhesions. This fact probably accounted for the patient's lack of shock or classic symptoms of rupture. The vertex was rotated anteriorly from the left occipito transverse position and delivery easily accomplished. The male infant weighed 6 pounds 11 ounces and was quite active. There was a superficial skin defect 1.5 cm. in diameter present over the lumbar region of the baby. One cubic centimeter of ergotrate was given intravenously; the placenta and membranes were easily delivered intact and complete. The lower uterine wall was blotter paper thin and the edges were ragged. In view of the poor condition of the tissues and the repeated rupture with repeated endangerment of the mother's life, it was decided to do a subtotal hysterectomy. The tubes and ovaries appeared normal and consequently were preserved. The infundibulopelvic ligaments were clamped on either side and incisions were made down the broad ligaments. The visceral peritoneum was then freed anteriorly above the cervix. The uterine arteries were clamped bilaterally and the top of the cervix incised removing the fundus. The cervix was closed with interrupted No. 2 chromic catgut sutures, the uterines ligated with the same, the ovarian pedicles secured with suture ligatures and tied into the cervical stump, and the raw surfaces peritonized. The peritoneum was closed with running No. 1 plain catgut. The muscles were united with interrupted No. 1 plain catgut, the fascia with figure-of-eight No. 1 chromic catgut, three silkworm-gut stay sutures were placed beneath the fascia and the skin closed with interrupted vertical mattress silk sutures. The patient remained in good condition through the operation and both she and the baby left the operating room in good condition, her blood pressure being 116/90 and pulse 98.

Immediately postoperative the patient received morphine sulfate grains $\frac{1}{6}$, a prophylactic blood transfusion of 500 c.c. of citrated blood and 700 c.c. of 5 per cent glucose in normal saline solution.

She remained in good condition until about five hours postoperative when she developed secondary shock with waxen color and cold clammy skin. She was mentally clear although her blood pressure dropped to 70/50 and the pulse rose to 140. A venoclysis of 10 per cent glucose

take place at 9 A.M. on March 22 but the patient had a silent rupture of the uterus an hour previous to operation. Professor S. J. Cameron, Regius Professor of Glasgow University, our consultant, performed the operation, and when the abdomen was opened it was found that the uterus was ruptured from the fundus anteriorly to the margin of the lower uterine segment and at the site of the old uterine scar. The rupture was very ragged and the child was lying free in the abdominal cavity as well as the placenta. The professor expressed the opinion at the time of operation that there was no hope, that the patient would probably be dead within an hour or so. He quickly sutured the opening and filled the abdomen with several pints of normal saline solution. The patient made an uneventful recovery, having been in the hospital for twenty-nine days after operation. The blood pressure was normal and the patient did not suffer from albuminuria."

On admission to the Methodist Episcopal Hospital prenatal clinic the physical examination was essentially negative, except for two separate intact lower abdominal midline scars and a "funnel" or anthropoid pelvis with measurements as follows: interspinous diameter, 26 cm.; intertrochanteric, 33 cm.; intercrural, 30 cm.; external conjugate, 20 cm.; a slightly narrow pubic arch; diagonal conjugate, 11.5 cm.; transverse of outlet, 7.0 cm.; posterior sagittal, 8.5 cm.; a hollow sacrum; a freely movable coccyx and bones of normal thickness.

Her prenatal course was essentially normal. She made 8 visits to the clinic between Sept. 9, 1940, and Dec. 26, 1940, during which time her hemoglobin dropped from 10.8 Gm. to 9.7 Gm. in spite of 5 gr. of ferrous sulfate three times daily. The serology was negative. All blood pressure readings were within normal limits. There was no albuminuria and her weight gain was only 9 pounds during that seventeen-week period.

She was seen and discussed by the senior staff on two occasions. The consensus of opinion was that she should be hospitalized at the thirty-sixth week and have an elective tertiary section. Further procedure such as sterilization or hysterectomy was to depend upon the operative findings.

Accordingly she was admitted to the hospital, Jan. 5, 1941, at which time a physical examination was essentially normal (No. 24210). The blood pressure was 134/86. The patient was in her thirty-sixth week and the fetus was estimated at seven to seven and one-half pounds in weight. The vertex presented in left occipitotransverse position and was floating. The cervix could not be reached on rectal examination. The fetal heart tone was normal. The two abdominal scars seemed intact, and there was no tenderness in them nor over the lower uterine segment. The usual laboratory workup was deferred to the following morning. The operation was planned for the seventh of January if everything was satisfactory.

The patient awoke at 3 A.M., Jan. 6, 1941, about twelve hours after admission, thinking her bowels had to move. After one unsuccessful attempt she noticed that the pain was recurring every five minutes. At 3:30 A.M. examination showed the uterus to be contracting with moderate intensity every five minutes. It was not relaxing normally between pains. The fetal heart sounds were normal, but the entire lower abdomen was acutely tender and seemed edematous. Morphine sulfate grains $\frac{1}{6}$ and scopolamine grains $\frac{1}{150}$ were given hypodermically at 3:45 A.M. and preparations were made for operation. The patient's general condition was good with blood pressure 124/80 and pulse 84.

domen toward the midline. Patient had lost about 30 pounds, was nervous, and had noticed palpitation and some shortness of breath. Her appetite was good and she had had some dysuria and frequency.

She had had pneumonia at the age of 6 which was complicated by empyema and had resulted in a rib resection.

Her father died of a carcinoma of the liver and her mother died of peritonitis following childbirth.

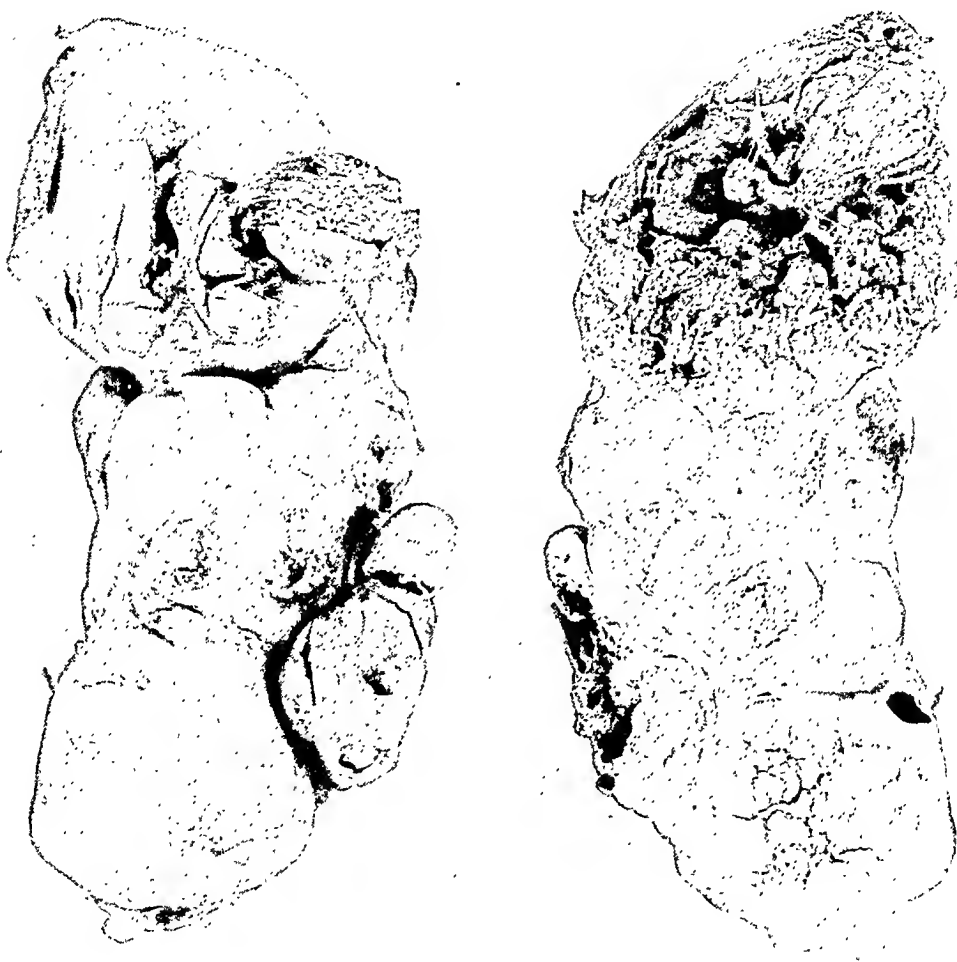


Fig. 1.—Photograph of the tumor shows (A) the kidney-shaped appearance, and extension of the tumor through the capsule. (B) Section surface of the tumor illustrates the nodular appearance and areas of hemorrhage and necrosis.

Marital History.—She had been married nine and one-half years; husband was living and well. She had had four normal pregnancies. Her menstrual periods started at the late age of seventeen years, and were regular every twenty-eight days, lasting seven to twelve days.

Physical Examination disclosed a well-developed, well-nourished white female who did not appear acutely ill. The temperature, pulse, and respiration were all within normal limits. The blood pressure was 115/70. The skin over the chest contained numerous vascular naevi. A healed scar was present in the left axillary region. The heart and lungs were essentially normal. The abdomen was diffusely tender. In the

was started and another 500 c.c. of blood was given within the hour. Following this treatment her condition became and remained satisfactory. A third transfusion of 500 c.c. of blood was given that evening; her highest temperature, 103° F., developed twelve hours later. After this her postoperative course was exceptionally smooth. A fourth and final transfusion was given on the fourth postoperative day (Jan. 9, 1941) and this raised her hemoglobin to 12.2 Gm. with 4.37 m. erythrocytes, 10,100 leucocytes and a differential of 69 per cent polymorphonuclears, and 31 per cent lymphocytes.

The wound healed by primary intention and the patient was discharged on her fourteenth day in good condition. The baby was discharged with the mother and weighed at that time one ounce less than its birth weight. No definite conclusion had been reached despite consultation about the lumbar skin defect other than that it was not a complete true spina bifida.

The patient returned for post-partum check-up at one month and six months and had no complaints. The wound was intact and the cervical stump was suspended in good condition.

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MALIGNANT DYSGERMINOMA OF THE OVARY

A Fatal Case With Autopsy

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REPORTS of fatal cases of dysgerminoma of the ovary with necropsy studies are very meager in the literature, and the report of even one additional case is deserving if it will add information to our present knowledge of the obscure malignant nature of this tumor. Too many of these tumors have been diagnosed benign clinically by the clinician whereas the pathologist for years has expressed a more pessimistic view, and his diagnosis of malignancy has often been challenged, as illustrated in the following case.

Case Report

History.—Mrs. P. O., aged 36 years, was first admitted to the South Shore Hospital in August, 1937, on the service of Dr. L. Lipschultz. At that time she complained of abdominal pains which had been present for three months. The pain was intermittent, sharp, stabbing, and generalized, and unrelated to her meals or menstruation. During this period she had noticed blood in her urine on two occasions lasting about ten days. (One month prior to her admission (1937) a mass was palpated in the ab-

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Course.—The patient made an uneventful recovery and was discharged Aug. 7, 1937. She was seen by Dr. McNatten Cook County Hospital) who gave the patient 18 high voltage treatments from Oct. 2, 1937, to Dec. 12, 1937, postoperatively.

Patient was readmitted to the South Shore Hospital (Feb. 12, 1940) two and one-half years later with complaints of pain on walking, marked weakness, and tenderness and distention of the abdomen during the past three months. Her weight was reduced from 150 to 116 pounds.

On physical examination the only noteworthy findings at this time were the distention of the abdomen, extreme tenderness, and an enlargement of the liver which extended down 4 fingers. The superficial veins of the abdominal wall were distended and prominent.

On Feb. 17, 1940, an exploratory operation was done. The liver and peritoneum were studded with metastatic nodules. Biopsy of one of the nodules revealed a similar picture to that seen in the ovary. Patient's condition became progressively worse. She was given palliative treatment and died April, 1940, three years after the onset of her symptoms.

Essential Autopsy Findings.—At necropsy patient was markedly emaciated. There were evidences of metastasis to the lungs, both kidneys, the liver, and peritoneum. A moderate ascites was noted.

Summary

A case of dysgerminoma of the right ovary in a patient 36 years of age is described. Three years subsequent to surgical removal, and following x-ray therapy patient died. At necropsy there were extensive metastasis to the peritoneum, the lungs, both kidneys, and to the liver.

COMPLETE HEART BLOCK COMPLICATING PREGNANCY

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COMPLETE heart block is so rare a complication of pregnancy as to warrant individual case reports. In 1935 Jensen¹ was able to collect only 14 cases from the literature, and recently Diddle² has added another. In the five years since the establishment of a Cardiac-Obstetrical Clinic at the Kings County Hospital, there have been 17,862 deliveries, but this is the first time we have encountered this complication. Although varying degrees of heart block are not infrequently seen, complete heart block with absolute dissociation of auricular and ventricular rhythms is distinctly uncommon.

Case Report

N. L. B., a 23-year-old colored primipara, presented herself at the prenatal clinic, Kings County Hospital, on Sept. 30, 1941. Her last menstrual period was on April 25, 1941, and her date of confinement was estimated to be Feb. 1, 1942. During the course of a routine physical examination, a systolic murmur was heard at about the level of the left fourth costal cartilage, close to the sternum and also at the apex. There

right pelvis a mass was palpated which extended to the right of the symphysis and was tender on deep pressure. Vaginal examination confirmed the presence of the mass in the right side. The clinical impression was an ovarian cyst.

Laboratory Findings.—The urine was negative. The blood showed a moderate anemia of 3,300,000 red blood cells.

On July 27, 1937, a bilateral salpingo-oophorectomy was done. The right ovary was transformed into a hard nodular tumor mass. The other ovary appeared normal, and a small amount of clear fluid was noted in the pelvis.

Surgical Pathology.—The right ovary formed a mass 16 by 8 by 6 cm. and was about the size of an adult kidney. (Fig. 1). The surface was nodular, and the capsule in places was interrupted by the nodes which were up to 6 cm. in diameter. Some were firm, others were soft and discolored purplish red. Other nodes on sectioning appeared light purplish gray with central areas of hemorrhage and softening.

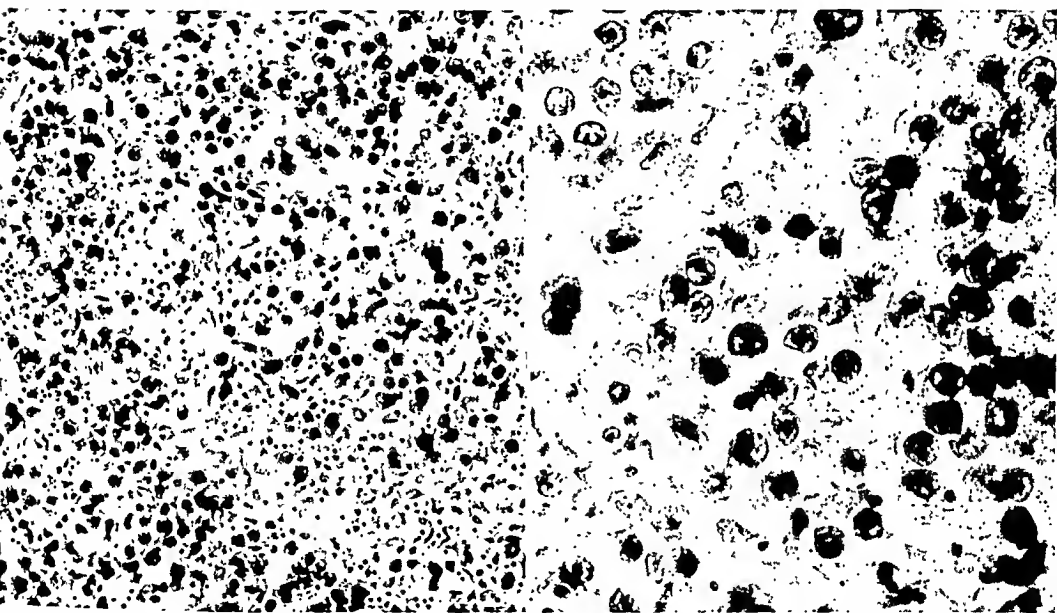


Fig. 2.—Photomicrographs of the tumor shows low and high power magnification. Note the cellularity of the tumor with its large polygonal cells containing oval and round hyperchromatic nuclei, some of which are huge and bizarre shaped. The stroma is sprinkled with small lymphocytes and contains a thin fibrillar septa.

Histologic Examination.—The tumor was very cellular and composed of solid masses of large polygonal and round cells with oval to round hyperchromatic nuclei and an ample granular cytoplasm. Many of the nuclei had nucleoli. Numerous mitotic figures were seen. The cells were often interrupted by narrow fibrillar septa infiltrated with small round cells. In places there were focal areas of hemorrhage and necrosis. The tumor cells resembled an embryonic germinal type of cell common for both the ovary and testicle.

Diagnosis.—Malignant dysgerminoma of the right ovary.

Deep x-ray therapy was recommended.

A section of the tumor at this time was shown to Dr. Walter Schiller who believed it was benign.

perium was uneventful and she was discharged from the hospital on Dec. 7, 1941. An electrocardiogram (Fig. 2) taken during her hospitalization was similar to the first electrocardiogram. At no time did she exhibit cardiac embarrassment or syncope. The patient was last examined at the cardiac obstetric clinic on Jan. 19, 1942, at which time the findings of the systolic murmur and electrocardiographic evidence (Fig. 3) of complete heart block were still present.

Complete heart block is an infrequent complication of heart disease. In an electrocardiographic series of 10,000 patients with cardiac symptoms or signs, examined between the years of 1916 and 1930 at the Massachusetts General Hospital, complete heart block occurred in 79 cases or an incidence of 0.79 per cent. It must be remembered that this included all age groups and both sexes. However, when these figures were analyzed by White and Jones,³ coronary artery disease was re-

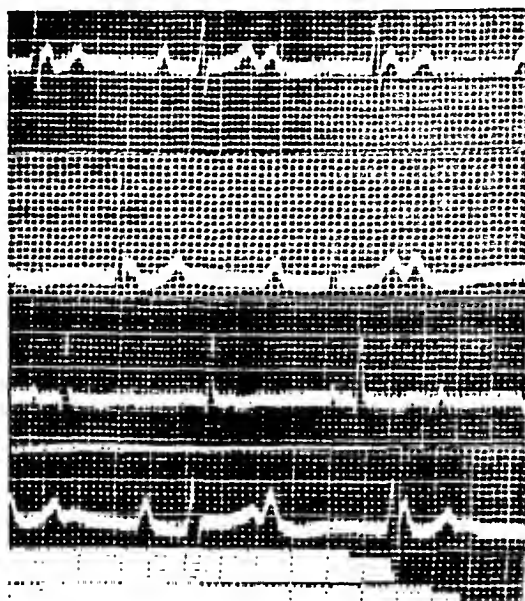


Fig. 3.—Feb. 6, 1941: Auricular rate, 100; ventricular rate, 62.

sponsible in 50.7 per cent; rheumatic infection in 27.5 per cent; congenital defects in 1; syphilitic involvement in 1; digitalis in 9; and an unknown factor (probably congenital) in 4 cases. Moreover, permanent heart block occurs twice as often in the male as in the female.

Coronary disease is rarely, if ever, encountered during pregnancy for it usually does not occur in women until they are beyond the childbearing age. Young women with long standing, severe rheumatic heart disease, the other most frequent cause for heart block, are likely not to marry or if married, not likely to become pregnant because of severe limitation of function which their cardiac state imposes upon them. Digitalis effect disappears when the drug is discontinued, and in this locality syphilitic cardiovascular disease in pregnancy is almost as rare as coronary disease. Thus one is left with a group whose etiologic factor is congenital or unknown. It is in this group that this patient has been classified.

Yater,⁴ in reviewing the subject of congenital heart block, states that the more important criteria for the diagnosis rests upon the electrocardiographic evidence of the block existing, the presence of a congenital

was a forceful apical impulse, but no thrills were felt. The rhythm was regular and the rate was 62. The blood pressure was 130/80. The lungs were clear and resonant. She had no complaints referable to the cardio-respiratory systems, but was directed to the cardiac-obstetrical clinic for further investigation of the murmur. A detailed history revealed that the patient had been perfectly well throughout her childhood. She denied ever being seriously ill and to the best of her knowledge had never suffered an attack of rheumatic fever, chorea, scarlet fever or diphtheria. She had never fainted. Physical examination confirmed the findings previously noted and a tentative diagnosis of congenital heart disease,

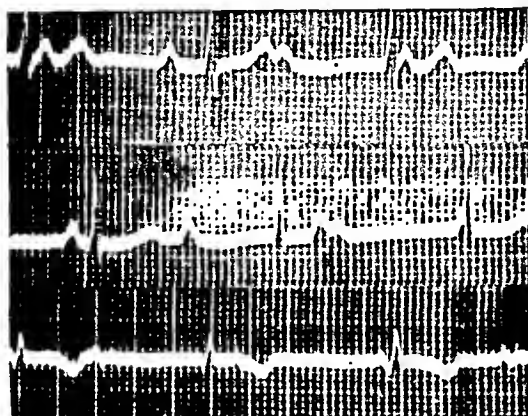


Fig. 1.—Oct. 20, 1941: Auricular rate, 100; ventricular rate, 62.

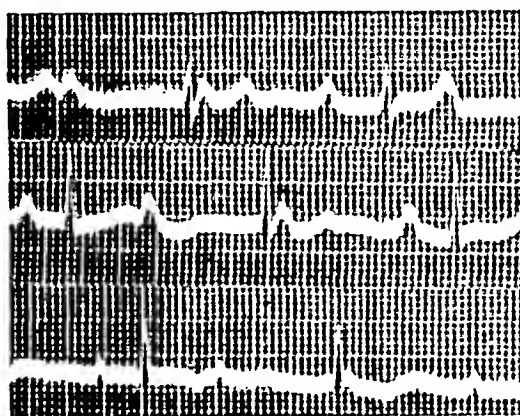


Fig. 2.—Nov. 27, 1941: Auricular rate, 100; ventricular rate, 62.

probably septal defect, was made. The blood Wassermann was negative. Roentgen examination of the heart revealed slight enlargement of the transverse diameter but no specific chamber enlargement. An electrocardiogram (Fig. 1) showed a complete heart block with a ventricular rate of 62 and an auricular rate of 100.

She was admitted to the Hospital on Nov. 24, 1941, because of moderate vaginal bleeding and mild symptoms of toxemia. She was put to bed and on November 29 went into labor and delivered spontaneously after seven hours a live colored male in good condition weighing six pounds and seven ounces. The placenta was delivered intact after ten minutes. The immediate post-partum condition was good. The puer-

turition begins as a result of a number of factors, structural, hormonal, nervous, nutritional and circulatory, which, at a time characteristic of each species and adapted to the morphologic condition present in each, are so associated that they lead to evacuation by the uterus of its contents."¹

One of the newer hormonal theoretical causes for the onset of labor is based on the sensitizing action of the uterine musculature by estrogen to the posterior pituitary extract.

Murphy² found that the uterus failed to respond to pituitrin before the twenty-fifth week of pregnancy in 32 cases in doses of 1, 2, or 3 minims. After this period the percentage responding increased weekly. Estrin blood levels have been observed to rise steadily after the fourth month (Smith and Smith) and to rise sharply just before the onset of labor (Runge, Seivers and Hartman³). There is a coincidental decrease in progesterone due to degeneration of the corpus luteum and changes in the placenta. Knaus observed that uterine muscle is refractory to the action of pituitary extract when corpus luteum activity is at its highest during the menstrual cycle. It seems logical to assume that, if the blood levels of the estrogens can be raised sufficiently, labor could be started by adding pituitrin. Jeffcoat³ in England and later Lubin and Waltman³ in this country observed an increase in contractility and mobility of the uterus following the administration of the natural estrins before labor; the latter with a dosage of 10,000 to 350,000 international units of progynon B were able to start labor in 8 women out of 36. Later, Peel⁴ in England reported the action of stilbestrol on labor in 79 cases divided as follows: In 52 it was given for two weeks before the calculated date of labor in an effort to prevent post-maturity, 24 (46 per cent) were considered successful when pregnancy terminated 280 days or earlier after the first day of the last menstrual period. Peel, however, concluded that its action in this capacity was disappointing, although he thought the cervix was softened and labor shortened when it finally began. The second group of 16 cases constituted those in whom an effort was made to induce labor, 3 of them had dead fetuses all of which terminated; of the remaining 13, 6 went into labor and 7 failed (46 per cent). Peel's routine was 10 mg. intramuscularly the day before and 1 mg. by mouth hourly for 10 to 12 doses the second day. In his third group of 11 cases, an effort was made to overcome uterine inertia with 4 successes.

In 1941 Abarbanel reported his observations in 21 cases in whom much larger doses were used orally as a primer before the usual induction of labor. He gave 10 to 15 mg. hourly for 10 doses followed in eight hours with a medical induction of castor oil and quinine. If labor did not ensue after a few hours small doses of posterior pituitary extract were given. He observed 9 successful inductions out of 10 cases (90 per cent) using this technique at or near term; complete success in 3 cases of missed abortion and labor, and complete failure in using the method to induce abortion in 5 cases. The remaining 3 cases were uterine inertia with 2 successes and 1 doubtful.

Personal Observations

For the past several months some of the waiting mothers on the Tulane Obstetrical Unit at Charity Hospital have received stilbestrol

heart lesion, namely, a patent interventricular septum, and the absence of any history suggestive of an infection that might have produced the block, e.g., diphtheria, congenital or acquired syphilis, rheumatic fever, or chorea.

The management of pregnancy in these cases and the prognosis is dependent upon the etiologic factor concerned. For the prognosis depends not so much upon the finding of the heart block as it does upon the cause and degree of functional limitation which the slow rate imposes upon the patient. In congenital lesions the cardiac musculature is unimpaired and the defect is often compensated for by hypertrophy of the heart. In addition, the ventricular rate in this group tends to be higher than is found in those secondary to arteriosclerosis or coronary artery disease. The combination of these factors explains the favorable prognosis. Since the majority of reported cases of heart block complicating pregnancy are congenital in origin and in these the ventricular rate is frequently above 50, the prognosis is good. Delivery should be effected in the usual manner and interruption of the pregnancy or sterilization of the patient in such cases is unwarranted.

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STILBESTROL IN THE TERMINATION OF PREGNANCY*

With Report of 21 Cases

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THE recent literature suggests that stilbestrol may be of value in the termination of pregnancy. Encouraging results have been reported by Jeffcoat, Peck, Lubin, Waltman and others. It is our purpose to review some of the more significant reports and present our experience with stilbestrol. Since this drug is now available at a cost which is not prohibitive, it seems that an evaluation of its present status in the termination of pregnancy would be timely as well as beneficial.

In the light of present knowledge, we are still in the dark as to the cause of the onset of labor, and are often at a loss to initiate it in the patient in whom one of the surgical methods is contraindicated, for fear of not being able to do a section later because of potential or frank intrauterine infection. Summing up the cause of the onset of this phenomenon, Reynolds said "there is no known single cause—as the numerous theories in the past imply. Rather, it now seems that par-

*Read at a meeting of the Louisiana State Obstetrical and Gynecological Society, New Orleans, Louisiana, April 27, 1942.

before or during a routine medical induction. Some of these have had it more or less haphazardly and without any standardization of dosage or technique. There have been some with dead fetuses in whom it was considered desirable to use the drug partly because of its supposed lactation inhibiting ability. More recently an effort has been made to follow a regular routine before and during the induction as follows: 10 mg. being administered 3 or 4 times daily for three days before the induction, and 10 mg. every hour following the usual dose of oil and enema. The results obtained by this technique are shown in Table I.

There were 28 patients who received the drug with the total dosage varying from 6 mg. to 720 mg. (150,000 to 18,000,000 international units). The latter case had two attempts. Beginning about three hours after the oil and enema, pitocin in small doses has been given routinely except in patients in whom labor had started. The criteria for success was labor within twenty-four hours after the last dose of stilbestrol on the day of the induction. Several (five) of the patients included in this study had 20 mg. three or four times daily for three or four days before the induction, and none on the day of the induction; in two of these, or 40 per cent, labor started. Of the 28 cases, there were 5 missed labor, or abortions with 5 successes; 22 in whom an effort was made to aid in the induction by using stilbestrol with 9 successes, or 41 per cent. There was one case of uterine inertia (Case 17) who was finally delivered with Dührssen's incisions.

In none of the cases was there an appreciable effect on lactation noted. Instead it had to be continued for a longer period to have any action. Nausea and vomiting were not noted in any of the patients, even those receiving large doses (720 mg.). Case 15 showed a moderate temperature reaction after and during its administration on two attempts. No explanation was found for this at either time.

We are still looking for a satisfactory medical means of initiating labor without subjecting the patient to possible vaginal and uterine contamination. Our problem is not the patient in whom vaginal delivery is certain, for in this group we feel that induction of labor has been satisfactorily solved, but in the patient in whom a trial is advisable before subjecting her to the dangers of a cesarean section. In this latter group are, (1) the patient with a borderline pelvis in whom a trial of labor seems advisable or maybe an early termination would mean a vaginal delivery, (2) the case of habitual death of the fetus at term, (3) the oversized baby with a possible relative disproportion, (4) cases in whom the cervix is too long for rupture of membranes, but need an induction for one reason or other.

This series is too small to make dogmatic statements, but in our hands the results appear to be less satisfactory than a simple medical induction, the ratio being about 40 to 50 per cent.⁵ Whether labor is actually shortened needs further study, but our series may suggest this. Its use does appear to be of value, however, in patients with dead babies, but most of these would probably go into labor spontaneously if left alone.

Summary

1. It seems likely that estrone plays a role possibly in the physiologic onset of labor, probably synthetizing the uterus to pituitrin. What the threshold of uterine activity is, is not known.

TABLE I. PATIENTS RECEIVING STILBESTROL

CASE	AGE	RACE	PARA	DURATION PREG.	INDICATION	TOTAL DOSAGE	LENGTH LABOR	DELIVERED	SUCCESS- FUL
*1	22	C	ii	Term	Mild tox.	380 mg.	Short	1 mo. later	No
2	23	C	i	Term	Waiting	720 mg. (2 times)	25½ hr.	3 days later	No
3	?	W	i	Term	Waiting	110 mg.	?	Day Ind.	Yes
4	20	C	i	Near term	Waiting	40 mg.	24 hr.	2nd day after	No
5	30	C	vi	Term	Waiting	240 mg.	1½ hr.	2nd day after	No
6	17	C	i	Term	Post-mature	220 mg.	31 hr.	48 hr. later	No
7	16	W	i	Term	Post-mature	60 mg.	7½ hr.	2nd day Pre. Ind.	Yes
*8	-	C	v	Term	Post-mature	280 mg.	2 hr.	Day Ind.	Yes
*9	-	C	ii	Term	Waiting	440 mg.	?	14 days later	No
*10	-	C	ii	Near term	Waiting	440 mg.	?	5 days later	No
*11	-	C	i	5½ mo.	Mild tox.	360	28 hr.	Day Ind.	Yes
12	-	C	i	Term	Mild tox.	100 mg.	-	2 wk. later	No
13	20	C	Mul.	Term	Mild tox.	260 mg.	9 hr. 4 min.	72 hr. after last	No
14	26	C	Mul.	Term	Uter. fib.	190	5 hr. 10 min.	2nd day Ind.	Yes
15	24	C	ii	Term	Isch. rec. abscess Post-mature	200 (1st try, No pit.)	No	No	No
16	22	C	iv	Term	Waiting	240 mg.	?	No	No pains with Pit.
17	?	C	Mul.	6 mo.	Uter. inert 4 days' labor	5 mg.	10 hr.	2nd day Dührssen	No
18	30	W	iii	8 mo.	Missed labor	120 mg.	?	3rd day Pre. Ind.	Yes
19	?	C	?	8 mo.	Missed labor	15 mg.	?	2nd day	Yes
20	?	C	?	Term	Stillborn	6 mg.	?	2nd day	Yes
21	38	C	Mul.	Post.	Missed labor	100	6 hr.	3rd day Pre. Ind.	Yes
22	32	C	Mul.	Term	Post-mature	160	9½ hr.	3 days later	No
23	20	W	i	Term	Waiting	130	9½ hr.	Day of Ind.	Yes
24	28	C	i	Term	Dead baby (2 attempts)	270	13 hr.	Day after 2nd attempt	Yes
25	19	C	i	Term	Term	230	2 hr. 8 min.	3rd day after	No
26	23	C	i	Term	Term	240	2 hr.	1 wk. later	No
27	18	C	i	Term	Term	260	9½ hr.	Day of Ind.	Yes
28	Case not successful, details not available, 200 mg. given								

*Cases in whom 20 mg. given every 4 hr. for 4 days before 40 per cent effective.

headache, vertigo, and visual disturbances, and began to vomit. These symptoms gradually increased in intensity and were accompanied by a noticeable loss of weight. The menstrual history was not available. It was stated that the patient had not noticed any fetal movements during the preceding two weeks; until that time the fetus had been active.

Physical Examination.—Blood pressure was 88/76; pulse, 140; and temperature, 99.6° F. The essential physical findings were coma, with Cheyne-Stokes respirations, nuchal rigidity, bilateral Babinski sign, crepitant râles in the left lung, and an abdominal mass. The abdominal mass was smooth, rounded, extended from within the pelvis to the level of the umbilicus and was considered to be the uterus. No fetal movements nor heart sounds were noted.

Because of the condition of the patient, it was not considered advisable to terminate the pregnancy by curettage. Spinal tap revealed a slightly turbid fluid containing 56 cells per c. mm. A pellicle formed on standing. Death occurred twenty-four hours after admission.

Autopsy Findings.—Bilateral tuberculous salpingitis with unilateral tubal pregnancy (five to six months), fetus dead; generalized caseous pelvic tuberculosis with multiple cold abscesses; tuberculous endometritis with decidual hyperplasia; generalized miliary tuberculosis of lungs, liver, spleen, kidneys, and adrenals.

Detailed Abdominal Findings.—Primary inspection of the abdominal cavity revealed the omentum extending downward toward the pelvis and adherent, in many areas, to all adjacent peritoneal surfaces. When the adhesions were separated there was noted a large, rounded, cystic structure occupying the greater portion of the lower abdomen. Its upper border was at the level of the umbilicus and its lower border was well within the pelvis. It measured 30.5 cm. in its greatest diameter, was oval in outline, and was centrally placed in the midline immediately above the uterus. Attached to its outer surface were many loops of bowel and omental adhesions. Grossly, this structure had the appearance of a thin-walled cyst; on closer examination it was identified as left tube, enormously distended, the wall in many areas being discolored, soft and friable, and undergoing early necrosis. During dissection, many small areas of the wall were perforated, resulting in the escape of a moderately thick, fluid exudate, some of which was blood stained. After incision of the structure, a fetus measuring 25 cm. in length (crown-heel) was removed. This fetus was apparently of normal development except the head which showed a moderately far-advanced degree of hydrocephalus. It was of female sex. There was extensive maceration of the entire skin surface. It was attached by the umbilical cord to the placenta which occupied roughly half of the inner wall of the tube in a hemispherical manner. Sections through the placental tissue revealed many old and recent blood clots which were undergoing liquefaction. The placenta was rather securely attached to the tube wall.

The opposite tube, at its origin from the uterus, was of normal caliber, but very quickly tapered out in retort shape; its lumen contained a large amount of a thick, creamy, yellow, caseous exudate. The uterus was slightly enlarged; the cervical os was patulous. The endometrium had a hyperplastic appearance but was uniform in quality throughout. The myometrium measured 3 cm. in its greatest thickness. The left ovary was intimately attached to the wall of the cystic tube by dense adhesions. There were many pockets of caseous exudate in and around

2. Stilbestrol may exert a similar action as suggested by Peel and Abarbanel when used at or near term. Peel was unable satisfactorily to prevent postmaturity in more than half of the cases in which he used it.

3. All are agreed that missed labor and abortion is its most useful field in termination of pregnancy. A total of 11 cases (including 3 in this series) having been reported with 100 per cent result.

4. As a part of the technique of medical induction its use has not been entirely justified in our hands. Our results, however, compare with those reported by Peel who used only stilbestrol.

5. Apparently it does not depress lactation to any marked degree when used pre- and intranatally, and most likely would have to be continued for a longer period after the birth of the baby to have this action.

6. Nausea and vomiting were not seen in any case, even with large dosage; however, one case showed an elevation of temperature after its use on two attempts.

We wish to acknowledge the aid of the E. R. Squibb Company for having furnished the greater part of the stilbestrol used in this study.

References

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4. Peel, J. H.: Proc. Roy. Soc. Med. 32: 1230, 1938-39.
5. Reddoch, J. W.: South. M. J. 29: 289, 1935.

TUBAL PREGNANCY ASSOCIATED WITH TUBAL TUBERCULOSIS

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(From the Butler County Memorial Hospital)

THE rarity of coexisting tubal pregnancy and tuberculous salpingitis has been emphasized recently in the reviews by Stevenson and Wharton¹ and Bland.² The latter, in reviewing the literature, found only 32 cases recorded and added one of his own. Rojel,³ in the foreign literature, has since recorded a similar case in a report not seen by us.

A most remarkable feature of the following case is the development of the fetus through five to six months of intratubal gestation.

Case History

N. W., housewife, primipara, aged 37 years, was admitted to the Butler County Memorial Hospital on Jan. 19, 1941, in coma, the onset of which occurred twenty-four hours previously. The history (from relatives) was incomplete.

The patient was approximately seven months pregnant and apparently well until one month before admission, at which time she developed

The remarkable fetal development through a five to six months' period probably resulted from previous tuberculous thickening of the tube wall, preventing earlier rupture.

References

1. Stevenson, C. S., and Wharton, L. R.: AM. J. OBST. & GYNEC. 37: 303, 1939.
2. Bland, P. B.: AM. J. OBST. & GYNEC. 40: 271, 1940.
3. Rojel, K.: Nord. Med. (*Hospitaltid*) 10: 1604, 1941.

320 EAST NORTH AVENUE

PRIMARY OVARIAN PREGNANCY WITH LIVING MOTHER AND CHILD

I. J. STRUMPF, PH.G., B.S., M.D., JACKSONVILLE, FLA.

(*From the Duval County Hospital*)

THIS is to report for record, a case of primary ovarian pregnancy where a full-term living child was recovered by laparotomy. It is obvious from a study of the meager literature that this type of implantation of an ovum is rare, and a fetus developing to full term and living is so much rarer that a report of such an occurrence is justifiable. Most of these ovarian pregnancies terminate in the first trimester by ovarian abortion and are found at laparotomy. A few have reached full term, unsuspected by the patient and attendant until labor has supervened. Here again the usual termination is death of the fetus following an unproductive period of labor.

Spiegelberg in 1879 laid down the following criteria for a diagnosis of primary ovarian pregnancy: .

1. The tube on the affected side must be intact.
2. The fetal sac must occupy the position of the ovary.
3. It must be connected to the uterus by the ligament of the ovary.
4. Definite ovarian tissue must be found in the walls of the sac.

It is obvious that in a full-term child the placenta would be of such size and the anatomic distortion so great that one or more of these criteria could not be fulfilled. However, sufficient anatomic and histologic evidence is presented to make certain the diagnosis here.

The comment of Von Winckel (quoted by Schorach)¹ concerning the high percentage of abnormalities noted in the babies at term carried as abdominal pregnancies is worthy of note. His figures run as high as 50 per cent. The child delivered as described below exhibited no evidence of abnormality.

The patient, an adult colored multipara (No. 141572), aged 25 years, whose first child was delivered at home uneventfully ten years ago, presented herself at the Duval County Hospital Clinic for prenatal care. There was no history of miscarriage or abortion. She had had chronic pelvic inflammatory disease. Her last menstrual period occurred on Feb. 28, 1941, the quickening on June 15, 1941; Kahn test was negative.

The first trimester was uneventful except for one incident which occurred on a visit to the clinic when she became nauseated and had ex-

the pelvic region and a cold abscess had extended subperitoneally along the lateral abdominal wall.

In view of the clinical and autopsy findings, it is highly probable that tuberculous meningitis also existed. Permission to examine the head was not granted. Microscopic examination confirmed the diagnoses, as listed, and tubercle bacilli were demonstrated in the tissues by special stain. An exhaustive, but unsuccessful, search was made for the organism within the chorionic villi. Unfortunately, the fetus could not be examined by section.



Fig. 1.—Cross-section through the placental site within the Fallopian tube. The thin, overdistended tube wall can be seen on either side of the placenta. The polypoid structure attached to the tube wall is a parovarian cyst.

The exact age of the fetus cannot be determined. However, based on its size and the history of approximately seven months' pregnancy, it can safely be concluded that the age of the fetus was at least between five and six months. It seems logical to assume that fetal development, in relation to age, was subnormal, the result of unfavorable placentation. Fetal death probably occurred two weeks before maternal death, when fetal movements stopped.

The inflammatory thickening and fibrosis of the tube wall, resulting from tuberculosis, probably accounts for failure of rupture much earlier in the pregnancy.

Summary

A case of tubal pregnancy associated with tuberculous salpingitis is reported.

Attached to one edge of this mass was the stump of the suspensory ligament of the ovary. The sac was incised and the spill suctioned while the baby was being delivered. Cord was clamped and cut. The child was full term and cried spontaneously upon delivery. The entire residual mass of placenta and membranes was lying free in the abdominal cavity without adhesion to intestine, or other abdominal viscera, and was removed by salpingo-oophorectomy. The vessels in the right infundibulopelvic ligament were huge and the stump required considerable ligaturing to get adequate hemostasis. The abdomen was closed routinely and the patient was returned to the ward.

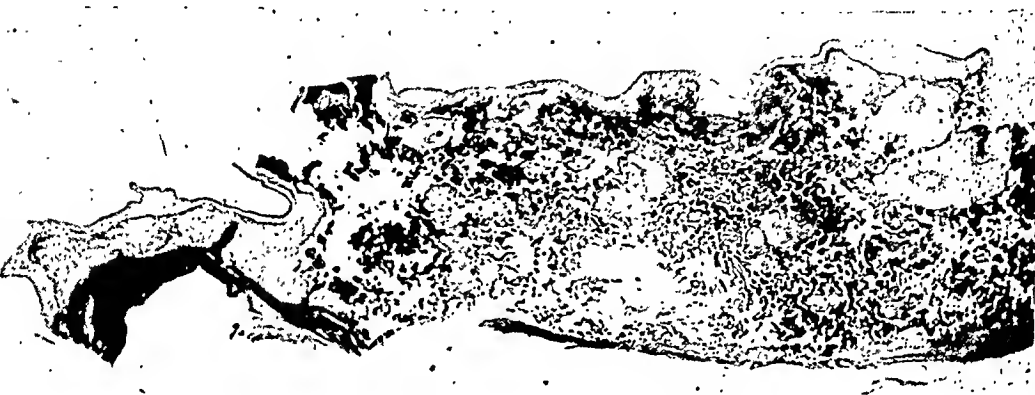


Fig. 1.—Low power view showing ovarian tissue and placental elements.

Her postoperative course was entirely satisfactory and both mother and child were discharged in good condition on the fourteenth day.

Pathologic examination as reported by Dr. L. Y. Dyrenforth, pathologist of Duval County Hospital, was as follows:

Gross: This specimen (No. 141572) consisted of a placenta with attached membranes and cord. The specimen presented several peculiarities: (1) The size was about 12 cm. in diameter and 4 cm. in thickness. (2) The umbilical cord was attached at the edge in a very unusual manner. (3) The amniotic membrane was thick and leathery, and it contained between its two layers remnants of placental tissue. (4) The large venous channels on the surface of the amnion were extremely prominent. (5) At one pole directly opposite the attachment of the umbilical cord there was a ragged mass containing many adhesions and fat. This was intimately adherent to the substance of the placenta. Sectioning through the latter at this point revealed a whitish firm area between the two surfaces of the placenta, but containing portions of placental tissue within it. These whitish areas occurred at many places within the substance of the placenta.

Microscopic: These sections apparently bear out the existence of ectopic gestation within the ovary. At least two structures, other than those that were intrinsically placental, were present. And these were so intimately a part of the pregnancy and its products that they could not be confused as artefacts.

In fact, the point of rupture seemed to have been included in the sectioning of the gross specimen and a definite, unmistakable rim of ovarian cortex appeared, thoroughly confluent as a growing and developing tissue, stretched over the characteristic placental structures: chorionic

treme pain in the right lower quadrant following a pelvic examination. She rested in the clinic for several hours and following this she was at home about a month with fever, nausea, and vomiting associated with lower abdominal pain. This subsequently cleared up and the balance of her prenatal course was fairly normal.

On present admission to hospital, Sept. 30, 1941, she claimed to have been in labor at home for about twelve hours with moderately severe regular "labor pains." On physical examination, the blood pressure was 130/80, Kahn was negative, and except for the abdominal examination, the findings were essentially negative. The abdomen was irregular in contour and the fetal parts were very readily distinguishable. The head was in the right flank, the fetal axis in the transverse position. X-ray confirmed this finding. There was considerable tenderness in the upper abdomen but no rigidity. There was cystic swelling in the epigastrium. Fetal heart tones were heard in the umbilical region, loudest on the left, rate 140. No contractions of uterus were palpated. On vaginal examination with aseptic precautions, the cervix was found to be soft and boggy but undilated, the external os admitting the tip of one finger.

Impression at this time was a full-term pregnancy with transverse presentation.

Course.—According to her own story labor had begun the day before admission, Sept. 30, 1941. She complained of pains coming fairly regularly every five minutes and now were hard enough to warrant her coming to the hospital for relief. She was in subjective "hard" labor until Oct. 1, 1941. During this day no evidence of progress in labor was noted, but the patient's pulse began to rise and she complained, in addition to her periodic labor pains, of a severe and persistent epigastric pain. She was also becoming markedly distended.

I was called in at this time to see her. The labor pains over a period of twenty minutes came periodically at approximately five-minute intervals. During these periods of "labor" no uterine contractions were made out, the fetal outlines were very readily palpable and the diagnosis of a transverse presentation was confirmed. There was continuous and severe epigastric pain. The patient was obviously suffering and her pulse had risen to between 140 and 160.

Vaginal examination at this time showed a long, thick, and closed cervix. There was no bleeding following examination and no sign of fibroid or other mechanical interference with descent and engagement of a fetal pole. The pelvis was ample for delivery. The condition of this patient was bad and rapidly becoming worse, and laparotomy was ordered for a probable abdominal pregnancy.

At operation under ethylpropane anesthesia, the abdomen was found distended and filled with thin-walled, purplish fetal membranes containing placenta and fetus at term. Uterus was soft, regular in contour, and smooth in outline, anterior in position, 3 to 4 times normal size. It was tremendously engorged with dilated vessels in right infundibulopelvic ligament. Placental encroachment and implantation in region of right broad ligament without any raw surfaces or attachments to uterus or gut. Left tube and ovary grossly normal. Greater part of omentum necrotic, amputated, caused apparently by impingement against pubic arch. Right ovary not recognized. Right round ligament normal. The removed specimen revealed membranes and complete, normal size placenta with smooth serosal-like covering throughout.

FRACTURE AND DISLOCATION OF BOTH SHOULDERS AS A RESULT OF ECLAMPTIC SEIZURE

EDWARD L. CORNELL, M.D., F.A.C.S., CHICAGO, ILL.

MRS. R. K., aged 22 years, para 0, gravida i, was admitted to Henrotin Hospital July 18, 1941. Her expected confinement date was Aug. 25, 1941. She had had prenatal care by her local physician for six weeks previous to admission. She had been on a salt-free diet for three weeks. On July 12, she was found on the floor in her home, unconscious after a severe convulsion. She was hospitalized in her home town and put under deep sedation and parenteral fluids. She remained comatose for seventy-two hours and had many convulsions.

She was not in labor on admission. She was markedly edematous and her vision blurred. Blood pressure was 220/130. The urine contained 4-plus albumin and hyaline and granular casts. She was unable to raise both arms at the shoulders. She also had considerable pain in the shoulders. The fetus was alive, but small in size. She looked very ill, "starved" and appeared to lack vitamins. On admission she was given 1000 c.c. of 25 per cent glucose, large doses of various vitamins, and a good meal. The next morning a low cervical cesarean section under local anesthesia was done and a live baby weighing 1,500 Gm. delivered. The baby was sent to a premature station. The placenta was badly infarcted and a beginning abruptio placentae was noted.

During the operation, the blood pressure varied from 190 to 220 systolic and 108 to 140 diastolic.

The patient made a good postoperative recovery until the ninth day when her temperature reached 100.2° F. and respirations rose to 28. The temperature gradually rose to 102.5° F. over a three-day period. An x-ray of the chest was ordered, and it was discovered that she had bilateral dislocation of the shoulders with comminuted fractures of the head of the humerus in the region of the greater tuberosity. The lungs were negative, also urine culture.

Dr. Charles B. Puestow reduced the shoulders under cyclopropane anesthesia. The temperature continued to range around 102° F. until August 19. In this interval a bronchopneumonia was diagnosed and treated with two courses of sulfathiazole. There was no apparent effect from the drug. August 12, there was pain in the left leg and an early thrombophlebitis was found. This gradually subsided after two weeks. Then the vein at the left elbow, which had been used for intravenous injections four weeks previous, thrombosed and caused a slight rise in temperature. This subsided within a week.

The patient's blood pressure gradually came down to 160/90, where it remained during the remainder of her stay in the hospital. She went home in an ambulance September 5.

The baby was in very good condition by the time the mother left the hospital and was taken home.

A recent communication (October, 1941) states that the mother has made a complete recovery and the baby is normal.

A review of recent literature and textbooks fails to reveal a similar case where the shoulders have been dislocated and fractured as a result

villi, hemorrhage, and bits of trophoblastic elements were broken off from the main mass. The whitish areas noted grossly were identified as infarcts, resulting from thrombosis of the branches of the umbilical vein.

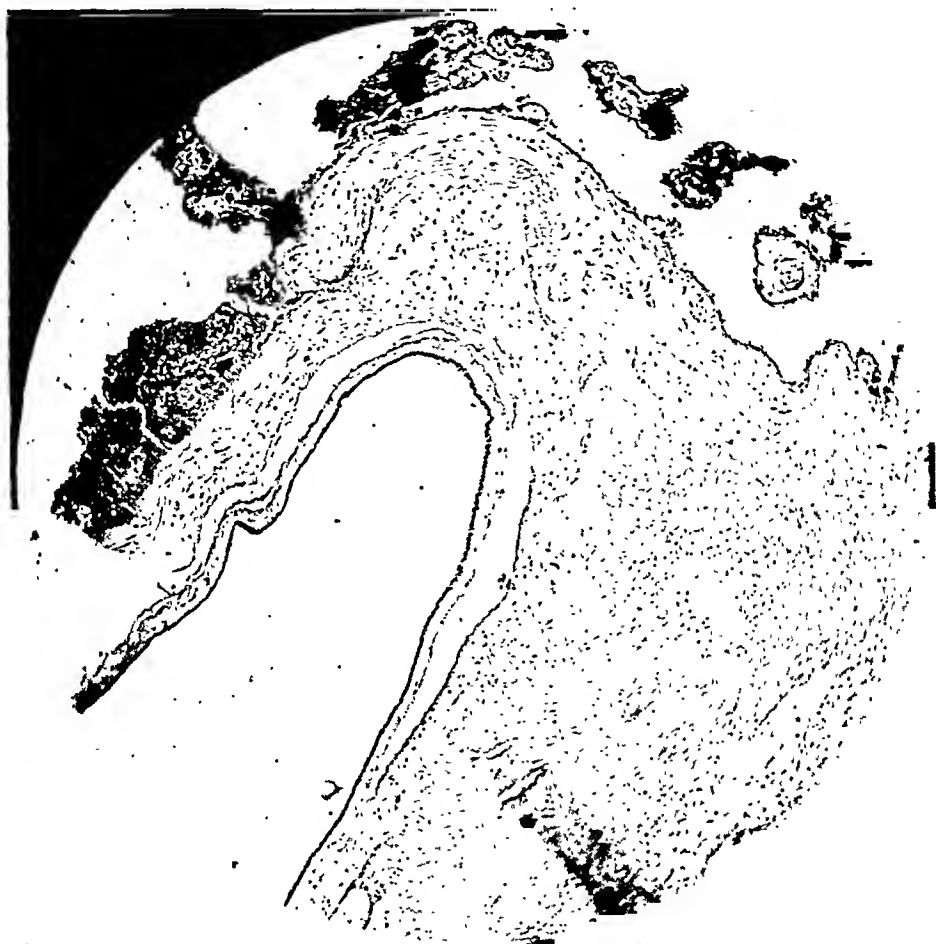


Fig. 2.—High power view of Fig. 1.

Other sections were being made, but I believe there was here incontrovertible proof of the existence of an ovarian pregnancy.

Diagnosis.—Ovarian pregnancy.

Acknowledgment is made to Dr. A. D. Stollenwoerck, Chief of the Obstetrical Service, Duval County Hospital, for the privilege of using this case from his service.

Reference

1. Schorach, W.: Arch. f. Gynäk. 162: 371, 1936.

base plate on the under surface prevents inversion and pinching of the posterior vaginal wall as well as limiting the excursion of the jaws.

A finger is introduced into the rectum and by careful palpation cervical dilatation and the station of the head are ascertained. While the index finger is so placed, the thumb and middle finger separate the labia, the vestibule is gently sponged with sterile cotton pledgets, and the sterilized instrument is introduced into the vagina with the jaws closed and the base plate pointing up. The tip of the base plate is introduced first; the handle is then depressed and rotated as it is advanced so as to bring the base plate posteriorly above the perineal body. The rectal finger then directs the tip to the center of the dilated cervix by pressure through the rectovaginal septum; the jaws are opened and the membranes grasped and severed. Forelying amniotic fluid protects the presenting part from the grasp of the instrument.

The criticism that this procedure might injure the cord is avoided by careful rectal palpation to insure that the presenting part is engaged and the cord is not presenting. The advantages to be derived from the use of this instrument lie in its simplicity and in the avoidance of an additional vaginal examination.

1540 EAST 53RD STREET

Erratum

In the article "Some Aspects of Early Human Development" by John Rock and Arthur T. Hertig, which appeared in the December, 1942, issue of the JOURNAL, line 1, on page 974, should read: "So far 60 women . . ." instead of "61 women," and line 13 should read "polypoid bit of mucosa." Delete the phrase "(Fig. 3)" which follows this in the published article. Fig. 3 refers not to ovum Be-7771, but to ovum Si-7699. On page 980, line 8 from the bottom should read "The former is three to five days younger than the latter . . .," instead of "three to four days . . ."

of convulsions. Since no one was present when the first convulsion occurred, we can only speculate how the accident occurred.

Cesarean section was done, because there was danger of losing the baby from abruptio placentae. The placenta was found partially detached.

122 SOUTH MICHIGAN AVENUE

AN INSTRUMENT FOR RUPTURING MEMBRANES*

EDWIN J. DECOSTA, M.D., CHICAGO, ILL.

THIS instrument was devised to serve two purposes: One, to simplify the conventional method of rupturing membranes following sterile vaginal examination; and two, to rupture membranes under certain conditions when it is deemed advisable to avoid vaginal examination.

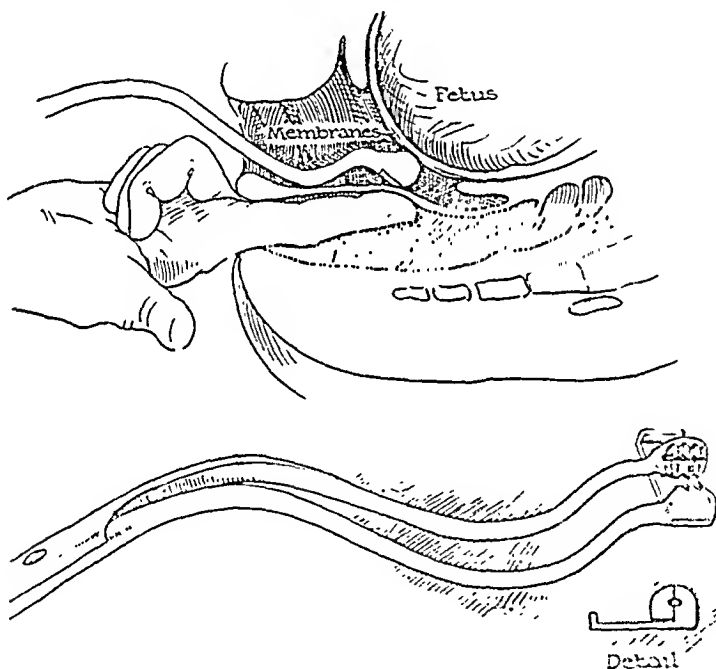


Fig. 1.

It is not the purpose of this communication to go into the indications or conditions necessary for rupturing membranes. Ordinarily, it is inadvisable to rupture membranes until after a careful sterile vaginal examination. There are occasions, however, when, with an engaged head and partially dilated cervix, one may not desire or consider it necessary to examine the patient vaginally. It is particularly for such circumstances that this instrument is presented.

The instrument illustrated in Fig. 1 possesses two curves: a pelvic curve A that follows the sacral curvature, and a cervical curve B that brings the biting edge into contact with the membranes and affords a convenient finger rest for properly directing these jaws. An angulated

*Presented at a meeting of the Chicago Gynecological Society, March 29, 1942.

Department of Reviews and Abstracts

Selected Abstracts

Gynecologic Operations

Dixon, W. C.: Retrovaginal Hernia, *Ann. Surg.* 115: 782, 1942.

The author reviews the literature on the subject with special reference to the incorrectness of many diagnoses because of the confusion in the criteria of what constitutes a true retrovaginal hernia. He points out the complications that may result from a failure in adequate diagnosis. The etiologic factors are also mentioned. The treatment is surgical since pessaries do not afford any relief. Two avenues of approach are mentioned, the abdominal and the vaginal. In addition the author gives a case report of a true retrovaginal hernia which was successfully operated upon.

WILLIAM BERMAN

Mattson, W. W.: Indication for Vaginal Hysterectomy in Treatment of Gynecologic Conditions, *Northwest Med.* 40: 11, 1941.

Vaginal hysterectomy has a valuable place in gynecologic surgery as a procedure offering many advantages in selected cases. Like any other operative procedure, however, it has its indications and contraindications. Mattson cannot share the enthusiasm of the surgeon who extends its usefulness to all surgical conditions of the pelvic cavity to the exclusion of the abdominal route which in some cases certainly is superior and far safer in the average surgeon's hands. When its use is limited to the correction of various stages of uterine prolapse of moderate-sized uterus in conjunction with reparative procedures of the pelvic outlet in women at the end of the childbearing period, the operation is safe, sound, and a boon to the patient and surgeon alike. Extended beyond this sphere, it may needlessly endanger the life of the patient as well as reflect discredit on the ability of the surgeon.

J. P. GREENHILL

Rendle-Short, Coralie: The Problem of Operation for Retroverted Uterus, *Brit. M. J.* 2: 649, 1941.

The author reports her series of 120 patients in whom the round ligaments were shortened for the correction of uterine retroversion.

A careful follow-up of these patients revealed that a perfect result, both anatomic and symptomatic, was obtained in only 50 per cent of the cases.

The author therefore suggests that a search for some other cause of the symptoms be made, and that a pessary be tried before resorting to operation.

In 19 patients with sterility in whom no other cause than retroversion could be found, 11 subsequently became pregnant.

FRED L. ADAIR AND RAYMOND L. YOUNG

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 20, 1942

The following papers were presented:

Hydradenoma Vulvae. Dr. W. C. Danforth. (For original article, see page 329.)

Gynecologic Aspects of Adolescence. Dr. Goodrich C. Schauffler, Portland, Oregon (by invitation).

An Instrument for Rupturing Fetal Membranes. Dr. Edwin J. DeCosta. (For original article, see page 355.)

MEETING OF APRIL 17, 1942

The following papers and case reports were presented:

The Importance of the Rh Factor in Transfusion Reactions. Drs. Edith L. Potter, Israel Davidson and Allen B. Crunden (by invitation). (For original article, see page 254.)

The Treatment of Vaginitis. Drs. Edward Allen and Hngo C. Baum (by invitation). (For original article, see page 246.)

A Pelvic Abscess Due to Lipiodol. Dr. Edward L. Cornell.

Fracture and Dislocation of Both Shoulders as a Result of an Eclamptic Seizure. Dr. Edward L. Cornell. (For original article, see page 354.)

MEETING OF MAY 15, 1942

The following papers were presented:

Clinical and Physiologic Correlations of Uterine Contractions. Dr. Louis Rudolph.

The Colostrum Intradermal Test for the Diagnosis of Pregnancy. Drs. Edward Allen (by invitation) and Lincoln B. Donaldson. (For original article, see page 208.)

Frank has no hesitation in strongly urging the profession to employ the non-operative method which he has developed, a method which is ambulatory, which produces no scars, and which, so far, has proved uniformly successful in establishing potentia coeundi and in restoring the self-respect and happiness of the afflicted individuals.

J. P. GREENHILL

Diaz, A. Rodriguez, and Anido, H.: *Surgical Considerations in Ten Cases of Total Hysterectomy and Cholecystectomy*, Rev. cubana de obst. y ginec. 3: 42, 1941.

The authors report a series of 10 cases in which both operations were performed simultaneously under spinal anesthesia. The cases were unselected and prophylactic appendectomy was also done. The morbidity was no greater than that in the authors' 300 cases of total hysterectomy. The authors feel that as a whole there is less physical and psychic risk in performing both procedures at one operation than in two separate operations.

R. J. WEISSMAN

Sunde, A.: *Experiences Gained From Operations on Vesicovaginal Fistulas*, Acta obst. et gynec. Scandinav. 21: 1, 1941.

In operating on cases of vesicovaginal fistulas, Sunde occasionally employs the prone position. He prefers a suprapubic fistula to an indwelling catheter if the catheter lies in such a way that it may injure the sutures. The most important point in the after care in operations for vesicovaginal fistula is leaving the indwelling catheter in place for a sufficiently long time. Most vesical fistulas should be operated upon vaginally.

J. P. GREENHILL

Daneff, G.: *A Method of Correction of Retroflexion and Hyperanteflexion of the Uterus*, Zentralbl. f. Gynäk. 64: 1462, 1940.

With the patient in the knee-chest position, the author opens the posterior fornix for the correction of hyperanteflexion or the anterior fornix for the correction of retroversion. A sufficiently large wedge of myometrium is excised at the most acute portion and the edges brought together with catgut, bringing the uterus into its proper position. The operation is done under local anesthesia and the patient may be ambulatory. Accidental incisions into the cervical canal give the author no alarm and cause no trouble. Hegar dilators may be used later with impunity. No statistics are given but the author recommends the procedure for correction of sterility and severe dysmenorrhea.

R. J. WEISSMAN

Items

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Wednesday, May 19, through Tuesday, May 25, 1943. The Hotel Schenley in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for reexamination in Part II must make written application to the Secretary's Office not later than April 15, 1943.

Fallis, L. S.: Management of Postoperative Wound Separation, *Surgery* 9: 198, 1941.

Fallis suggests that conservative nonoperative treatment be more widely adopted for treating disrupted abdominal wounds. A review of all the cases of such wounds at the Henry Ford Hospital up to and including the year 1935 gives the mortality rate of 34 per cent; 70 per cent of the patients who died did so within twenty-four hours of being subjected to secondary closure. It seems that at least in certain cases the operation itself was a determining lethal factor. Therefore alternative methods of management should receive serious consideration. Since 1936, 27 cases of wound disruption have been treated; they occurred among 4,153 laparotomies. The mortality rate was 37.3 per cent; but what is significant is the evidence in favor of non-operative treatment. Seven of the 16 patients whose wounds were resutured died, a mortality of 43 per cent, but only three of the 11 whose wounds were strapped with adhesive tape died, a mortality of 27.3 per cent. Henceforth the author states that secondary suture has gradually been abandoned until, in the last two years, all disrupted wounds occurring in the general surgical service of the Henry Ford Hospital have been treated by packing and adhesive strapping, with excellent results.

J. P. GREENHILL

Frank, Robert T.: Evolution of the Treatment for Absent Vagina, *J. Mount Sinai Hosp.* 7: 259, 1941.

Absence of the vagina is a fairly common malformation found in otherwise perfectly normal feminine individuals. The vulva appears entirely normal. On separating the labia, a dimple or small blind pouch in the region of the hymen, varying in depth from one-quarter to 3 cm., is usually found, although recently Frank encountered a case where no depression was present. Rectal examination, as well as exploratory laparotomies, have shown that in almost every instance the uterus is represented by a small, solid, muscular rod with tubes and ovaries. The ovaries are usually normal, and corpora lutea have repeatedly been found.

The author has encountered more than 30 of such individuals and of these, 12 have been subjected to hormonal studies.

In this group of over 30 females with absence of the vagina, the great majority showed normal feminine habitus. The sex urge in both the married and unmarried women of this group was definitely within normal range.

The time for any intervention is preferably between eighteen and twenty years. A number of patients had already planned to marry.

Frank has always been impressed by the ease with which it was possible to separate rectum from urethra after incision of the hymen and superficial fascia. Those who have reported any operation for establishing an artificial vagina will have noted that the septum can be separated with two or three sweeps of the finger up to the peritoneal reflexion.

In 1935 an individual presented herself in whom there was a deep dimple, apparently the result of vigorous attempts at coitus. Anyone familiar with the ease with which the septum between urethra and rectum in absence of the vagina can be separated by the introduction of two fingers after the hymeneal membranes have been incised, must have been impressed by the resilience and softness of these tissues. This had repeatedly impressed the author as encouraging. In this first case, therefore, the author had the patient introduce heavy glass tubes, first of small diameter, later increasingly larger, and to the author's surprise and gratification, within a few weeks a canal, seven and a half centimeters in length, was developed. Since then eight further cases have been completed by this simple, nonoperative, ambulatory method of treatment.

Correspondence

Convulsions Following the Administration of Pituitary Extract

To The Editor:

Drs. Sullivan and Hefferman have raised a most important point and one urgently requiring attention when they caution against the intravenous administration of postpituitary extract to toxemic women. In their observation reported in the October, 1942 issue of this *JOURNAL*, the injection of 50 mg. ephedrine preceded the spinal anesthesia; one ampoule of ergometrine was given following the advent of sharp occipital headache in the wake of the administration of postpituitary extract. The blood pressure rose from 130/70 to 210/110.

In a paper presented in 1932 at the Chicago Lying-in Hospital, evidence pointing to the controlling position of the pitressin principle in the pathogenesis of the late toxemia of pregnancy was carefully collected and analyzed. Clinical observations and laboratory findings were correlated and fused to a single end. It was emphasized that, "the use of commercial preparations of postpituitary for the stimulation of uterine contractions during or after labor is contraindicated in pre-eclamptic and eclamptic conditions" (*AM. J. OBST. & GYNEC.* 26: 311, 1933).

Interest at present focuses on functional disturbances of the vascular tree as probably holding the key to the intriguing mystery of the mechanism underlying the syndrome termed late toxemia, with augmented responsiveness of the arterioles to the postpituitary principle as the final determinant in pre-eclampsia. As epitomized in two recent papers (*Western J. Surg.*, Nov. 1941; *Cincinnati J. Med.*, May 1942), the constitutional alteration of the normal pregnant organism as the result of the hyperplasia and associated overactivity of the endocrine chain, adrenal cortex, thyroid, pituitary, as well as the abundance in the blood of estrogenic and gonadotrophic hormones and certain split-products of proteins, serves to produce intrinsic vascular hypertonus and increased reactivity to pitressin. Storage in the normal placenta of significantly large quantities of acetylcholine as Nature's device designed to counterbalance these vascular abnormalities, was viewed as the focal point in safeguarding both the maternal and placental circulation. Dislocation of this equilibrium as the result of placental acetylcholine deficiency, figures as the fundamental argument in our new concept, radically different from current thought. Complete abandonment of the traditionally axiomatic idea of the elaboration in the placenta of "toxins" as the primary seat of the disorder, and of renal ischemia as a vital etiologic factor, signifies the radical departure.

Eloquent evidence, in favor of the basic concept of *placental deficiency* as a strategically placed element in the pathogenesis of toxemia, has recently been adduced by the researches of Nixon and Wright, showing a significantly lower concentration of vitamin B₁ in the toxemic placenta (*Brit. M. J.*, p. 604, 1942); and of Nisino, revealing the absence of vitamin C in eclampsia (*Chemical Abstracts*, 35: 2187, 1941).

I incline to the belief that this new concept represents a scientifically articulate explanation of all the anatomic, chemical, and clinical aspects of the disorder under consideration. Regarding the observation of Sullivan and Hefferman, it should be borne in mind that the vasopressor effect of pituitary extract was intensified by the preceding use of ephedrine, while ergometrine to all appearances acted here as the precipitating factor in the causation of the convulsions, the arterioles having been conditioned to any vasoconstrictor agent. In many hundred

The Pittsburgh Obstetrical and Gynecological Society will hold a subscription dinner meeting at the Hotel Schenley, on Saturday evening, May 22, 1943, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary of the Society, at 121 University Place, Pittsburgh, Pa. An interesting program is being provided.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board. Applications are now being received for the 1944 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons

Rules Governing the Award of the Foundation Prize

1. "The award which shall be known as 'The Foundation Prize' shall consist of \$150.00."

2. "Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery."

3. "Manuscripts must be presented under a nom-de-plume, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the nom-de-plume and containing a card showing the name and address of the contestant."

4. "Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis."

5. "The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the Journal of the Author's choice. Unsuccessful contributions will be returned promptly to their authors."

6. "Three copies of all manuscripts and illustrations entered in a given year must be in the hands of the Secretary before June 1st."

7. "The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation."

8. "The President of the Association shall annually appoint a Committee on Award, which under its own regulations shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting."

JAS. R. BLOSS, M.D., Secretary.
418 Eleventh Street, Huntington, W. Va.

Necrology

HOWARD ATWOOD KELLY, Baltimore, Md., January 12, 1943, at the age of 84. Noted gynecologist, writer, author, and teacher. Founder of the Kensington Hospital in Philadelphia and assistant professor of obstetrics at the University of Pennsylvania. Then joined the faculty of Johns Hopkins in Baltimore as professor of obstetrics and gynecology (1889-1899) and for the next twenty years as professor of gynecology. A pioneer in the use of radium for the treatment of cancer, he founded the Howard A. Kelly Hospital in Baltimore in 1892 with its store of five grams of the element.

HERMANN JOHANNES BOLDT, New York, N. Y., January 12, 1943, at the age of 87, in St. Petersburg, Florida. Gynecologist. Born in Germany. He came to the United States in 1865, graduated from the New York University Medical College in 1879 and from 1890 to 1923 was professor of gynecology at the New York Postgraduate Medical School.

instances of intravenous administration of postpituitary extract for the treatment of uterine atony following expulsion of the placenta, I never observed generalized convulsions. Indeed, this procedure has saved the life of the parturient woman on innumerable occasions, as emphasized in a special article in this JOURNAL, September, 1938. In view of the recent interesting communication by Dr. James Young (*J. Obst. & Gynaec. Brit. Emp.*, June, 1942), pointing to the histologic evidence of areas of placental disintegration in mild cases of toxemia, it would have been desirable to have the placenta of the case under consideration examined microscopically. The concept of a sustained balance between blood pressure raising and restraining principles in the pregnant organism may offer an explanation for the presence of subclinical forms of toxemia, attended with normal blood pressure but with potential damage to the placental storage of the active vasodilator. Viewed in this way the interesting case reported by the authors may fall in this category.

In conclusion, may I sound a warning note against the use of ergometrine in toxemic women, bearing in mind the blood pressure raising effect of this drug. Cases on the brink of toxemia are on record in which no pituitary extract was given, but an alkaloid of ergot, followed by violent generalized convulsions.

J. I. HOFBAUER, M.D.

CINCINNATI, OHIO
DECEMBER 4, 1942.

Vitamin C in Abortions Associated With Blood Dyscrasia

To the Editor:

The article appearing under the heading "Correspondence" as a letter from Dr. Lyman Burnham in the November issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY prompts me to report the results of a case treated with large doses of vitamin C by mouth, as well as intravenously (100 mg. twice a week). This medication was given because of a previous six and one-half months' miscarriage (August, 1941), at which time bruised areas, typical of those seen in people lacking vitamin C, were noticed on the fetus in spite of the complete absence of trauma. It was also ascertained at that time that the father was Rh positive and the mother Rh negative.

Notwithstanding vitamin C medication, as well as vitamin K administered both by mouth and by intravenous injections, and intravenous injections of calcium gluconate, this patient again miscarried at twenty-two weeks on Sept. 30, 1942.

The intravenous route was chosen for the vitamin C medication as the patient had consumed large amounts of orange juice during her previous pregnancy, and it was assumed that she might not have absorbed this from her intestinal tract.

Another patient whose first pregnancy ended at six and one-half months and her second at six months had a third pregnancy terminate last May at three months, notwithstanding intravenous vitamin C medications, vitamin K and calcium gluconate, as described above, having been given during the third pregnancy.

This therapy was used although in a personal communication from Dr. Louis K. Diamond of the Children's Hospital in Boston, he stated that he considered that vitamin C would be of little value in this pathologic physiology.

In the first case mentioned above a 50 mg. pellet of progesterone was inserted at twenty-one days (as soon as the Friedman was reported as positive), and another at four months.

WESTBURY, N. Y.
DECEMBER 1, 1942.

ROBERT S. MILLEN, M.D.

Lee-Jones (*Fundamentals of Good Health*¹) estimates that one physician, devoting 2,000 physician hours per year, could care for all the obstetrics in a community with a population of 7,332, with 23.56 pregnancies per 1,000 general population. These writers state that this does not allow for anything other than the time actually spent with the patient. They further estimate that 100 pregnancies will result in 86 deliveries (83 live births and 3 stillbirths), while 14 will abort. Of the 86 terminating in birth, they feel that the general practitioner can deliver all but nine, who require an obstetrician.

TABLE I. FROM LEE-JONES' FUNDAMENTALS OF GOOD HEALTH (IN 1932)

		PER CENT OF ALL CASES REQUIRING MEDICAL CARE	PER CENT OF ALL PHYSICIANS' HOURS
Puerperal state		2.52	14.05
Female genitourinary		1.71	2.56
Total		4.23	16.61
	PHYSICIAN HOURS PER 100,000 POPULATION. TIME ACTUALLY SPENT WITH PATIENT	PHYSICIANS REQUIRED	
		PER 100,000 POPULATION	FOR UNITED STATES
Prenatal care	8,611	4.31%	5,293
Delivery and post- partum care	18,660	9.33%	11,457
Total	27,271	13.64%	16,750

Table I from Lee-Jones shows that 4.23 per cent of all patients are obstetric-gynecologic and consume 16.61 per cent of the practitioner's time. However, their estimate of the time actually spent with the patient might be compared with the time needed for the management of an industry to sign a contract to supply a customer. The actual signing of the contract is insignificant as compared with the time and study needed in the preparation of the contract and all details appertaining thereto. They estimate that the time required for prenatal care will require of the physician 3.66 hours per patient, while delivery and post-partum care by the physician will require 7.92 hours per patient. While these figures represent only the estimated time actually spent with the patient, who will render the decision when such split-second timing will require that such service be rendered? It would seem that such deliveries would have to be made on a time schedule, and where and how is the practitioner trained to make such decisions?

The Associated Press in July, 1942, quoted figures from the Federal Procurement and Assignment Service showing that 89,862, or 51 per cent, of the 176,200 physicians in the nation are listed as specialists. In 1930, there were 40,000 specialists, or about 30.5 per cent, among 112,000 physicians.

In the care of patients, it is taken for granted that every graduate is capable of doing general practice at the time of graduation; that he is competent to practice general medicine, pediatrics, surgical diagnosis,

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American Association of Obstetricians, Gynecologists and
Abdominal Surgeons

Fifty-Fifth Annual Meeting, September 10 to 12, 1942

PRESIDENTIAL ADDRESS

FACTORS INFLUENCING THE GEOGRAPHIC DISTRIBUTION OF THE OBSTETRICIAN-GYNECOLOGIST*

GRANDISON D. ROYSTON, M.D., ST. LOUIS, MO.

ON THIS, the Fifty-Fifth Annual Meeting of our Association, we find the very existence of the nation and every one of our people gravely threatened. Regardless of the outcome of this struggle, it is evident that our lives will be changed radically in the future. As members of a thoughtful profession, we can, we must, we will adjust ourselves to the needs of our country and of our people.

Dr. Palmer Findley, a former president, suggested to me last year that the geographic distribution of the obstetrician-gynecologist might be of interest as the subject of my address to you at this time. Although this subject seemed at first rather remotely connected with medical education, it has proved otherwise. The growing tendency of the government to provide medical care, to which our profession has seemed somewhat indifferent, indicates the importance of a more serious consideration of the problem.

The Directory of Medical Specialists, in its last edition, published in 1940, shows that although 11.3 per cent of the total population of the United States resides in cities with a population under 5,000 as compared with 12.3 per cent residing in cities of over 1,000,000, the latter have nine to ten times the number of certified specialists.

*Presidential address at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., September 10 to 12, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

mailing list of the American Congress of Obstetrics and Gynecology, and the Directory of the American Medical Association.

It is recognized that all of those questioned do not limit their work, yet their various affiliations and connections with the sources from which the lists were compiled, indicate their interest in the specialty. It was felt that a direct expression from physicians actually doing this work throughout every state would be more illuminating than to investigate through educational groups. The latter have too often seemed less closely in touch with the realities faced by the practitioner.

Almost two-thirds (1,405 of 2,156) of all communities questioned had a population of less than 10,000, thus denoting that our specialty occupies an important part in the work of the practitioners residing there. Lee-Jones' estimate is that 16.61 per cent of all physician hours are devoted, as follows: to puerperal state 14.05 per cent; to female genito-urinary diseases 2.56 per cent.

The Committee on Graduate Medical Education of the American Medical Association gives the figures in 1936 for those physicians limiting their work or giving special attention to a specialty as follows: obstetrics 2,437; gynecology 1,169; obstetrics and gynecology 3,792; a total of 7,398. The figures here presented are an attempt to canvass all of this list and also all practitioners having interest in the specialty.

The results of this study are shown in the following tables. Table II shows the number and population of each community questioned as well as the number of practitioners questioned. As might be expected, the larger communities were less numerous, and had the greater number of practitioners questioned.

TABLE II

REPRESENTED IN QUESTIONNAIRE	TOTAL	NO. WITH POPULATION OF:					
		UNDER 10,000	10,000- 25,000	25,000- 50,000	50,000- 100,000	100,000- 200,000	OVER 200,000
Communities	2,156	1,405	395	165	95	53	43
Practitioners	8,766	1,631	819	672	719	872	4,053

Table III shows that of the age group under 40, the greatest proportion were reared in communities with a population under 10,000, yet a smaller incidence than in the other two age groups (40-59, and those of 60 years and older). This may have been due to the fact that more of the younger age group were reared in larger communities where many of them remained to practice. Many of this group located in communities where they attended medical school or interned.

Tables IV and V show the trend of more than half to practice in communities other than that in which they were reared. This change is mainly to larger communities. Forty-one and eight-tenths per cent of the men under 40, 54.7 per cent of those from 40 to 59, and 68.6 per cent of those of 60 and over, were reared in communities under 10,000 population. Hence, it is evident that the majority of those in our specialty were reared in smaller communities.

minor surgery, and first aid in emergencies, and normal obstetrics, subjects stressed for the intern year. This is wishful thinking when our medical schools now graduate men not yet safe practitioners of the branches mentioned, and who aspire to become specialists before they have had this basic training. If the practitioner will avoid all meddling interference in obstetric cases and, if in any doubt as to what course to pursue, will do nothing, the end results will be generally good. The great majority of all difficulties encountered in obstetrics result from unwise interference. For this reason, it is the responsibility of medical schools to graduate only those fully competent to diagnose, discriminate, and treat properly such a large proportion of normal obstetric patients.

The gynecologic care of patients by the recent graduate of today is naturally influenced by his training in medical school. Most of this training is in the care of gross pathologic conditions and operative cases, hence the tendency to consider every patient an operative case. Too little time and thought are given to functional disturbances which the Committee on Medical Education states may be due to or aggravated by social and economic conditions. The judgment and management of gynecologic patients by the general surgeon or the general practitioner often lead to abortive and misdirected procedures for which no skill in technique will compensate. Many schools are wisely using their out-patient departments for such teaching, though too often the great weakness of the modern medical school is in its failure to utilize to the fullest extent the services of experienced clinicians for this purpose. The present-day graduate is more often a laboratory adherent than a close clinical observer. It is believed by many experienced practitioners that an out-patient service approximates closely conditions seen in private practice, yet in obstetrics the present tendency is to reduce the number of home deliveries, where the student and intern can learn to manage normal labor most readily.

The incidence of operated patients applying in an out-patient gynecologic service varies from 3 to 10 or 12 per cent. These figures might be improved, should every hospital require that a written diagnosis and proposed procedure be publicly displayed in the operating room prior to operation. Such a rule would prove highly beneficial in the interest of the patient, the diagnostic study by the operator, and the teaching of interns and students.

The material for this study, an analysis of which I am presenting, is taken from questionnaires mailed to 8,766 physicians in 2,156 different locations. These practitioners either limited their work to, or manifested special interest in, this specialty. The mailing list was obtained from compiling the mailing lists of all national, regional, and available special societies of obstetricians and/or gynecologists, the Diplomates of the American Board of Obstetrics and Gynecology through 1941, the

TABLE VI

AGE GROUPS	TOTALS		NO. LIVING IN LOCALITIES WITH POPULATION SIMILAR TO PLACE REARED		NO. MOVING TO LOCALITIES WITH POPULATION DIFFERENT THAN PLACE REARED	
	NO.	%	NO.	%	NO.	%
Under 40 yr.	939	31.6	493	52.5	446	47.5
40-59 yr.	1,610	54.3	730	45.3	880	54.7
60 yr. and over	417	14.1	172	41.2	245	58.8
Totals	2,966	100.0	1,395	47.0	1,571	53.0

TABLE VII

POPULATION GROUPINGS		NO CHANGE IN LOCATION OR POPULATION STATUS (IN PER CENT)			MOVED TO COMMUNITY WITH CHANGE IN POPULATION STATUS (IN PER CENT)		
		UNDER 40 YR.	40 TO 59 YR.	OVER 60 YR.	UNDER 40 YR.	40 TO 59 YR.	OVER 60 YR.
Under 10,000		9.5	18.8	37.8	8.5	3.7	5.3
10-25,000		7.1	6.0	5.8	13.7	10.2	15.1
25-50,000		6.3	5.2	5.2	12.3	13.2	10.6
50-100,000		7.3	6.9	3.5	18.4	12.3	11.8
100-200,000		9.3	10.1	5.8	10.8	16.0	9.8
Over 200,000		60.5	53.0	41.9	36.3	45.6	47.4
Total	% of total	35.3	52.4	12.3	28.4	56.0	15.6
	No.	493	730	172	446	880	245
	No. in group	1,395			1,571		

TABLE VIII

CHOICE OF PRESENT LOCATION WAS INFLUENCED BY:	TOTALS		AGE GROUPS (IN PER CENT)		
	NO.	% OF TOTAL (2,966)	UNDER 40 YR.	40 TO 59 YR.	OVER 60 YR.
Desirable hospitals	1,492	50.3	27.8	57.8	14.4
Desirable professional connections	1,281	43.2	29.5	56.3	14.2
Home town	1,077	36.8	32.0	56.6	11.4
Desirable environment to rear family	934	31.2	26.1	55.0	18.9
Location near relatives	710	24.0	32.7	53.2	14.1
Desirable teaching connection	700	23.6	31.8	54.6	13.6
Opportunity to make money	641	21.6	25.6	53.5	20.9
Environment suitable to health	373	12.6	21.2	52.3	26.5
Desirable group practice	229	7.7	33.1	52.0	14.9
Other reasons	214	7.2	27.6	53.8	19.6

Among the younger group, desirable group practice, location of near relatives, and home town influenced the choice of present location, in the order named. Among the older group (60 and over), an environment suitable to health, the opportunity to make money, and a desirable environment in which to rear a family were the most common factors influencing the choice of present location.

Among all age groups, the opportunity to make money ranked sixth. Other reasons were a desirable place in which to live, climate, cultural attractions, recreational opportunities, etc., while three wrote "to get away from wife's relatives."

Tables IX, X, XI, and XII show the factors indicated in the order of choice for making smaller communities more desirable locations. All

TABLE III. AGE GROUPS UNDER FORTY YEARS

REARED IN COMMUNITY WITH POPULATION OF:	TOTALS		MOVED TO COMMUNITY WITH POPULATION OF (IN PER CENT):					
	NO.	% OF TOTAL	UNDER 10,000	10,000 TO 25,000	25,000 TO 50,000	50,000 TO 100,000	100,000 TO 200,000	OVER 200,000
Under 10,000	186	41.8	0	15.6	14.0	21.5	9.7	39.2
10-25,000	79	17.7	13.9	0	12.8	15.0	11.4	46.8
25-50,000	56	12.6	14.3	8.9	0	25.0	14.3	37.5
50-100,000	31	7.0	9.7	16.1	16.1	0	12.9	45.2
100-200,000	28	6.3	14.3	10.7	7.1	7.1	0	60.7
Over 200,000	65	14.6	20.0	24.6	21.5	21.5	12.3	0
Totals	No.	445						
	%	100.0	8.8	13.0	12.8	18.4	10.6	36.4

TABLE IV

REARED IN COMMUNITY WITH POPULATION OF:	TOTALS		MOVED TO COMMUNITY WITH POPULATION OF (IN PER CENT):					
	NO.	% OF TOTAL	UNDER 10,000	10,000 TO 25,000	25,000 TO 50,000	50,000 TO 100,000	100,000 TO 200,000	OVER 200,000
Under 10,000	481	54.7	0	13.1	12.4	13.5	14.3	46.6
10-25,000	146	16.6	6.2	0	17.1	9.6	13.0	54.1
25-50,000	71	8.0	5.6	11.3	0	16.9	16.9	49.3
50-100,000	58	6.6	5.2	6.9	13.8	0	22.4	51.7
100-200,000	54	6.1	11.0	1.8	16.7	7.4	0	63.0
Over 200,000	70	8.0	15.7	20.0	20.0	18.6	25.7	0
Totals	No.	880						
	%	100.0	3.7	10.2	13.2	12.3	14.9	45.7

TABLE V. AGE GROUPS OVER SIXTY YEARS

REARED IN COMMUNITY WITH POPULATION OF:	TOTALS		MOVED TO COMMUNITY WITH POPULATION OF (IN PER CENT):					
	NO.	% OF TOTAL	UNDER 10,000	10,000 TO 25,000	25,000 TO 50,000	50,000 TO 100,000	100,000 TO 200,000	OVER 200,000
Under 10,000	168	68.6	0	18.4	12.5	11.9	8.9	48.2
10-25,000	27	11.0	18.5	0	11.1	11.1	18.5	40.7
25-50,000	22	9.0	13.6	13.6	0	4.6	4.6	63.6
50-100,000	5	2.0	20.0	0	0	0	40.0	40.0
100-200,000	9	3.7	0	0	0	11.1	0	88.9
Over 200,000	14	5.7	28.6	21.4	14.3	28.6	7.1	0
Totals	No.	245						
	%	100.0	5.3	15.1	10.6	11.8	9.8	47.4

Table VI shows the replies accordingly to the age groups of those who remained in localities similar to those in which they were reared as well as the number who changed.

Table VII shows the present distribution of practitioners replying to the questionnaire. This suggests that there are opportunities and needs for trained obstetricians and gynecologists in communities with populations ranging from 25,000 to 200,000.

Table VIII shows the factors that influenced the choice of present location. Desirable hospital facilities ranked first among the total replies, followed by desirable professional connections, home town, etc.

able consultation in other branches. Where the choice of factors was indicated by a check of several factors and was not enumerated, all factors checked were given equal importance in the tabulations. A desirable place in which to live or to rear a family, and desirable climate were also considered important factors, as well as desirable religious environment, and by no means least was the expressed desire to locate where there are many physicians who will refer patients.

TABLE XI. AGE GROUPS OVER SIXTY YEARS

FACTORS	TOTALS		ORDER OF CHOICE (IN PER CENT)								
	NO.	% OF TOTAL	1	2	3	4	5	6	7	8	9
Adequate hospital facilities	345	16.9	83.5	10.1	2.0	2.6	0.3	0.9	0.6	0	0
Environment economically able to support specialist	272	13.3	62.5	15.1	11.7	5.9	2.2	1.1	1.5	0	0
Congenial professional associations	261	12.8	51.0	6.1	10.3	8.4	7.3	11.5	2.7	2.7	0
Ample transportation facilities	250	12.2	57.2	18.0	7.2	5.2	5.2	2.4	3.6	1.2	0
Accessibility to medical centers	234	11.5	52.6	4.7	7.2	9.0	6.0	9.0	8.5	3.0	0
Proximity to good schools	215	10.5	53.9	1.4	6.5	5.1	8.0	6.0	6.5	12.6	0
Public trained to cooperate with specialist	215	10.5	49.8	7.4	16.8	14.4	3.7	2.3	3.3	2.3	0
Economic stability	211	10.3	49.3	7.6	7.6	10.0	16.1	4.7	3.8	0.9	0
Other desirable factors	40	2.0	67.5	10.0	5.0	2.5	2.5	5.0	2.5	5.0	0
Total No. of choices in 417 replies	2,043	100.0									

TABLE XII. FACTORS INDICATED IN ORDER OF CHOICE FOR MAKING SMALLER COMMUNITIES MORE DESIRABLE LOCATIONS (TOTALS, ALL AGES)

FACTORS	TOTALS		ORDER OF CHOICE (IN PER CENT)								
	NO.	% OF TOTAL	1	2	3	4	5	6	7	8	9
Adequate hospital facilities	2,412	16.9	72.6	13.6	7.4	3.8	1.5	0.6	0.4	0.1	0
Environment economically able to support specialist	2,079	14.5	48.5	23.1	14.0	6.9	3.1	2.2	1.5	0.7	0
Public trained to cooperate with specialist	1,890	13.2	38.4	16.4	19.0	11.1	6.1	4.7	2.6	1.7	0
Congenial professional associations	1,769	12.4	32.4	7.7	11.9	15.1	12.3	11.7	6.1	2.8	0
Accessibility to medical centers	1,611	11.3	31.5	4.8	10.4	11.3	11.5	11.3	14.0	5.1	0.1
Ample transportation facilities	1,581	11.0	31.6	18.5	12.7	11.8	9.4	7.0	5.9	3.1	0
Economic stability	1,475	10.3	27.1	8.7	14.6	16.1	14.9	10.0	6.1	2.4	0.1
Proximity to good schools	1,236	8.9	29.2	1.9	5.6	6.4	9.1	10.0	13.6	24.0	0.2
Other desirable factors	216	1.5	53.7	5.1	4.6	6.5	2.8	2.8	2.3	4.6	17.6

Specially trained obstetricians and gynecologists seem to obtain their patients largely from one of three sources: (1) referred by other phy-

TABLE IX. AGE GROUPS UNDER FORTY YEARS

FACTORS	TOTALS		ORDER OF CHOICE (IN PER CENT)								
	NO.	% OF TOTAL	1	2	3	4	5	6	7	8	9
Adequate hospital facilities	719	16.9	60.1	18.4	11.0	6.5	2.2	1.1	0.7	0	0
Environment economically able to support specialist	641	15.0	46.5	23.7	15.1	6.4	3.3	3.1	1.3	0.6	0
Public trained to co-operate with specialist	638	14.9	38.7	20.5	18.0	10.8	4.9	3.9	2.1	1.1	0
Congenial professional associations	538	12.6	26.6	9.9	12.6	13.9	15.6	13.4	5.6	2.4	0
Accessibility to medical centers	459	10.7	23.3	5.5	11.3	13.9	12.4	11.6	17.7	4.1	0.2
Economic stability	451	10.6	19.8	10.6	17.5	16.9	15.5	11.5	6.4	1.6	0.2
Ample transportation facilities	450	10.5	20.1	13.5	15.0	14.9	11.8	9.3	10.7	4.7	0
Proximity to good schools	330	7.7	16.1	1.8	5.8	6.1	8.5	12.4	15.1	33.6	0.6
Other desirable factors	46	1.1	39.1	4.4	6.5	6.5	2.2	2.2	4.3	10.9	23.9
Total No. of choices in 939 replies	4,272	100.0									

TABLE X. AGE GROUPS FORTY TO FIFTY-NINE YEARS

FACTORS	TOTALS		ORDER OF CHOICE (IN PER CENT)								
	NO.	% OF TOTAL	1	2	3	4	5	6	7	8	9
Adequate hospital facilities	1,348	16.9	76.1	12.0	6.8	2.7	1.5	0.3	0.3	0.1	0
Environment economically able to support specialist	1,166	14.7	46.4	24.6	14.0	7.4	3.2	1.9	1.7	0.8	0
Public trained to co-operate with specialist	1,037	13.0	35.8	15.7	20.1	10.7	7.3	5.6	2.8	2.0	0
Congenial professional associations	970	12.2	30.6	6.9	12.1	17.6	11.8	10.8	7.2	3.0	0
Accessibility to medical centers	918	11.6	30.3	4.6	10.8	10.6	12.4	11.5	13.6	6.2	0
Ample transportation facilities	881	11.1	30.2	21.2	13.1	12.2	9.3	7.0	4.2	2.8	0
Economic stability	813	10.2	25.3	8.1	14.9	17.2	14.1	10.6	6.5	3.3	0
Proximity to good schools	691	8.7	27.8	2.2	5.2	6.9	9.8	10.1	15.1	22.9	0
Other desirable factors	130	1.6	54.6	3.8	3.8	7.7	3.1	2.3	1.6	2.3	20.8
Total No. of choices in 1,610 replies	7,954	100.0									

age groups agree that first, adequate hospital facilities must be available; and second, the environment must be economically able to support a specialist, while a public trained to cooperate with a specialist, congenial associations and accessibility to medical centers, closely followed. The older age group place ample transportation facilities fourth among their choices. It is emphasized in many of the private comments that congenial professional associations are desired not alone for personal and professional contacts in obstetrics and gynecology, but also for avail-

tion. Such perfection in one individual rarely exists. The result has often been disillusionment and disappointments to all parties concerned. The rare individual with a truly creative mind and love for research should receive every facility for pursuing his investigations. In my opinion, he should receive the highest salary among his colleagues of similar rank in his institution. Too often his talent as an investigator is not well utilized, while his time is dissipated by too many hopeless demands of minor consequence.

It is indeed a poor criticism that offers no suggestion for improvement. It is probable that medical schools of the future will receive less endowment and in some instances may be forced to obtain governmental aid to exist. If such aid is to be forthcoming, medical schools must realize and really discharge their functions better if they are to justify the reasons for their existence. The present outlook for adequate financial support from private sources is doubtful, and the necessity of governmental aid may have to be considered. This aid is likely to depend upon the ability of the medical schools to graduate an adequate supply of capable physicians for ample medical care to every community. The following suggestions are offered with this hope:

1. The office of dean should receive sufficient salary to attract a capable executive and administrator, who will devote full time to the office. He should be thoroughly familiar with all that transpires in every department. He must insist that every departmental head organize his department properly and work harmoniously with all other departments to the benefit of his institution and its products (students, alumni, research, etc.). He should interpret the medical school to the public.

2. Departmental heads should be selected on the basis of their ability to excel in the branch they expect to teach. The basic science branches should be headed by men expert in such branches, while clinical departmental heads should be primarily expert clinicians and executives with full appreciation for research. They should see that every member of their departments makes some annual contribution. With few exceptions, our specialty has been taught best by those who were primarily good clinicians. Perhaps less than 2 per cent of the student body is interested in, or capable of, developing into research investigators, and medical schools should be more cognizant of this fact in the interest of the more than 98 per cent of students who are being trained to treat sick people.

3. In view of the vast field of medicine and the general recognition of the inability of any medical school to graduate in four years a man safe to practice medicine, thirteen states in this country and four Canadian schools (up to 1939) require a fifth year of internship before graduation. On all sides may be found criticisms of the late age at which men in full possession of their faculties become fully active

sicians; (2) through institutional connections; (3) referred by well-satisfied former patients. Although customs vary in different communities, in most instances the last source is easily the most dependable and least likely to undergo changes. References from other physicians are likely to be from one's contemporaries, and when the ripeness of age and experience should be most desirable for the patient's welfare, often many of the contemporaries have died, ceased to practice, etc. Institutional sources of supply may sometimes require too much political effort to maintain oneself.

This inquiry has attempted to reach every practitioner in the United States listed as being interested or specializing in obstetrics and/or gynecology. The response of more than 33 per cent is encouraging as compared with the customary 25 per cent of responses reckoned by statistical institutions. In addition to the replies tabulated, a number could not be used for reasons of being too incomplete, death of party addressed, illegibility, and one reply from West Virginia stating, "This is the silliest of all silly questionnaires I have ever seen; it is not worth an answer." All other responses were helpful and cooperative.

Eight hundred and sixty-six, or more than 29 per cent of the replies brought additional voluntary information varying from a few words to letters of several pages. These voluntary comments suggest that the background, education, and preparation of the physician often may exert a marked influence on his choice of location. Many replies state, "I attended medical school and located here; these are the reasons for my present location." Another stated "after being regimented through medical school and hospital for nine or ten years, I felt the need of being told what to do, so remained where I could be directed." Another, aged 31, wrote, "I am afraid to get away from the place where everything has been planned for me." Such statements raise the question as to whether the present medical school is developing in its graduates the proper initiative. The general belief is that the function of the medical school is to train doctors to treat sick people.

The Commission on Graduate Medical Education, consisting of twenty representative educators, was organized in 1937 and published its report in 1940. This report recognized that the stress and strain of modern society cause functional disturbances, often of social and economic origin, or aggravate them, that may mask or simulate organic disease. How much this is being taught to students today is debatable. This report advocates that the intern year should be used for training in general medicine, normal obstetrics, pediatrics, surgical diagnosis and first aid in emergencies, while surgical technique should be reserved for the residency.

The modern medical school seems to have demanded of a departmental head: (1) the production of investigative work; (2) that he be an able teacher; (3) a capable clinician; (4) an executive; (5) have ability to satisfy the trustees, public, etc., and often raise money for his institu-

work into two and one-half or three calendar years is best suited for emergencies, since vacations are needed to prepare the student for the work ahead under normal conditions.

3. Scholarships or loan funds should be made available for every needy student who shows unusual ability or interest in investigative work. It must not be forgotten that clinical research, as emphasized by Heaney in commenting on Sampson's work on endometriosis, is fully as important as chemical research.

4. Every student, following four years' work in medical school, shall serve two additional years of rotating internship including out-patient work in a hospital under the supervision of his medical school before graduation. This would necessitate closer affiliation between the medical schools and the hospitals of their communities to their mutual advantage. This experience is as desirable for the medical school as it is for student or intern. It would make possible the graduation of better trained physicians *really competent* to be safe general practitioners at an age not necessarily greater than that at which they now graduate without an internship. Residencies and assistant residencies can be used to perfect the training of the specialist. Such specialists would be better trained because of this compulsory two-year rotating internship and externship that too few of them now have.

If the medical profession desires to provide adequate medical care for *all* the people of this country, the suggestions just made offer a way to make a safe and competent general practitioner of every graduate when he receives his diploma.

The results of the analysis of this questionnaire indicate that we cannot hope to have an equitable geographical distribution of certified specialists in every community. However, we can insure that every practitioner has received adequate training for safe obstetric and gynecologic care before graduation. Such universal training should qualify every graduate, wherever he locates, as an asset in our field.

Let us hope that a sane and practical solution of our problem will keep our profession out of the realm of the politician and of political control. A better geographic distribution of better trained practitioners is essential to this end.

I am indebted to my secretary, Miss Helen Schroeder, for compiling and arranging this mailing list as well as other helpful and laborious work. Classifying and tabulating the return replies was done with the help of my helpmate, Eunice W. Royston.

Reference

1. Lee, Roger F., and Jones, Lewis W.: *The Fundamentals of Good Obstetric Care*, Chicago, 1933, University of Chicago Press.

members of their communities. Professor H. C. Sherman has pointed out that by the time a professional man has finished his schooling, about one-third of his life has passed; another third will be spent in proving to himself and to others what he is able to do, and in most cases not until he is approximately fifty years old does he attain to a post of high responsibility and is given the fullest opportunities to do his work.

Professor H. C. Lehman has found that the majority of outstanding contributions by physicists, chemists, and inventors were made at 30 to 34 years of age. His investigation convinced him that the prime of life occurred in adolescent or early adult life, and he concluded that the greatest mental productivity was on the average recorded at the age of thirty.

The present-day graduate from medical school is not now able to begin private practice until this late age. The undesirability of such prolonged preparation has been sounded by President Lowell of Harvard University and President Butler of Columbia University, while President Hutchins of Chicago University feels that in many instances the collegiate education should terminate at the end of two years. Dr. J. P. Simonds of Northwestern University in the June, 1940, issue of the *Marquette Medical Review* sounded a highly pertinent note when he stated that the general practitioner, of all of our citizens, can do more to save medicine from socialization than any other group. This threat looms much more ominously over us today than in 1940, yet it is doubtful if our medical schools are fully alive to this danger of political control.

The value of a college education prior to admission to medical school requires no argument. The results speak for themselves in all walks and professions. With no desire to lower standards, yet with an earnest hope to improve the training of medical graduates who should spend more of their time being trained in the work that they expect to do, I would like to see every student admitted to medical school only on the following basis:

1. Individual selection, preferably after a personal interview by a personnel committee on admissions. Such committees could be appointed by each medical school, and interview each applicant at stated times and places similar to specialty board examinations. The applicants might be graded A, B, C, and the results pooled through a common clearing house of all the schools. If possible, the college and the high school should collaborate with the medical school in the applicant's preparation through the last two years of high school and the first two years of collegiate work. Some mistakes in admissions will always occur, yet individual selection after a personal interview together with the applicant's past record, should limit these errors.

2. Applicants would be eligible for admission to medical school after two or more years of college work. The crowding of four years' collegiate

here. On the days that the radium is not in the uterus the patient receives x-ray therapy.

The factors used in the production of the roentgen ray are 800 kilovolt maximum obtained from a double pulsating villard current, a load of 10 milliamperes on the x-ray tube, which is rendered gas free by oil vacuum pumps, a water-cooled tungsten target, a filter equivalent of 10 milliamperes of copper, a focal skin distance of 70 or 86 cm., field sizes varying from 10 to 20 square cm., and a half value layer of 8.2 mm. of copper, corresponding to an average wave length of 0.028 or a minimum wave length of 0.0128 angstrom unit. The output of roentgens per minute measured with a thimble chamber is 36 roentgens without and 44 roentgens with backscatter. The dose attained at a depth of 10 cm. measured in a bakelite phantom is 56 per cent of the surface intensity if the size of the entrance field is from 300 to 400 square cm. Whenever practicable the number of fields is two, namely pubic and sacral. If the patients had an anteroposterior diameter of 23 cm. or more, three or four fields were used. The amount of radiation required to produce a tolerance skin dose with 800 kilovolt roentgen rays is 4,000 roentgens if applied in ten fractions at forty-eight-hour intervals. If two fields are used, the midpelvic dose is the same as that attained on the skin, or about 4,000 roentgens, at the lateral bony pelvic walls as well as in the mid-pelvis. The rate of recovery of the tissues after each fractional dose has not been subtracted. The rate of recovery of the normal tissues in contradistinction to the abnormal ones is as yet not known. The dose attained within the pelvis after twenty-eight days was 4,000 roentgens, with backscatter.

Clinical Grouping

The clinical grouping of Schmitz¹⁶ was used to classify these cases as to the extent of the disease.

Clinical Group I.—The cancer is clearly localized. The growth not larger than 1 cm. in diameter may be said to be clearly localized. The uterus is freely movable. The form and consistency are normal.

Clinical Group II.—The tumor is about 2 to 3 cm. in diameter. The uterus is freely movable. Palpation elicits an area of infiltration or nodulation in the walls accompanied by a corresponding increase in size of the body.

Clinical Group III.—The tumor invades about one-half of the body. The size is perceptibly increased and irregular. The consistency is firmer than normal, especially within the planes of the growth. Subserous nodes are felt plainly. The mobility of the uterus is decreased, the inguinal or hypogastric lymph nodes may be enlarged but are movable.

Clinical Group IV.—Comprises the totally carcinomatous uterus with invasion of the adjacent structures, especially the parametria and lymph nodes. There is fixation of the tumor mass and the metastases. Fixation is always characteristic of advanced and terminal cancers.

Method of Studying the Removed Uteri

At the time this report was in preparation there were available for detailed study four of the five uteri, in which after radiation no tumor could be found microscopically in routine sections. These four uteri

THE EFFECT OF PREOPERATIVE IRRADIATION ON ADENOCARCINOMA OF THE UTERUS*

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IN 1935 a Y-shaped radium filter was described¹⁵ which we feel was an improvement over the methods in vogue at this time.^{1-3, 5, 9, 13} The equal intensity curves and the calculation of the radium dose in roentgens were given. Since this method was adopted in our clinic, 77 patients with adenocarcinoma of the uterine fundus have been admitted to our service. It was, therefore, considered of interest to study these cases to determine the effect of this type of irradiation on the carcinoma and to compare those patients who were irradiated by what we considered an adequate dose with those inadequately treated according to our standard.

Material Studied

Of the 77 patients 11 were hysterectomized after various time intervals following irradiation treatment and the effect of the irradiation on the tumor and the uterus was studied. Five of these patients were considered adequately treated according to our described technique and in none of these uteri was carcinoma found. The remaining 6 cases, inadequately irradiated, in our opinion, all showed carcinoma. Twenty patients were irradiated but not hysterectomized. Ten of these had one or more curettages to determine the presence or absence of active disease. Again it was the finding that those cases treated according to our technique were most likely to be free of detectable carcinoma. A third group of 7 cases had been diagnosed as adenocarcinomas by other pathologists but we were unable to obtain tissue for grading or verifying the diagnosis. In each instance, however, the referring physician was considered dependable. Five in this group had curettage following irradiation and one had a panhysterectomy. The remaining 39 cases were excluded from this study because they were hysterectomized and then irradiated.

Technique of Adequate Irradiation

All patients are curetted and the Y capsule containing 50 mg. of radium element in each arm is immediately inserted into the uterine cavity. The width of the uterine fundus has been determined and the capsule opened as described in the original article. After 2,000 mg. hours the capsule is removed. On the eighth and sixteenth days this radium dose is repeated. This gives a total radium dose of 6,000 mg. hours. The isodose curves and r. dose have been published and will not be repeated

*Read at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 10 to 12, 1942.

TABLE I. SUMMARY OF CASES RECEIVING PREOPERATIVE RADIATION THERAPY

PATIENT AGE GROUP	DIAGNOSIS ON CURETTINGS	RADIUM AND X-RAY	INTERVAL BE- TWEEN RADI- ATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
A. D. 50 II	Adenocarcinoma Grade II	6,000 mg. hr. Y caps. 4,000 r. x-ray midpelvis	4 months	Vaginal hysterectomy. Bilateral salpingo- oophorectomy	Nerotic polypoid mass $2 \times 1 \times 1$ cm. attached in left cornu; chronic cervicitis. Radiation changes. Healed salpingitis. Atrophic ovary. No malignant tumor microscopically	Living and free of detectable disease, 4 yr. 8 mo.
D. C. 38 III	Adenocarcinoma Grade III	2,000 mg. hr. Y caps. 4,000 r. x-ray midpelvis	8 months	Panhysterectomy. Bilateral salpingo- oophorectomy	Ulcer with necrotic margins and base in body just above internal os. Adjacent 5 mm. of myometrium necrotic. Chronic cervicitis. Radiation changes. Left hydrosalpinx. Atrophic ovaries. No malignant tumor microscopically	Living and free of detectable disease, 2 yr. 3 mo.
M. S. 65 II	Adenocarcinoma Grade II	6,000 mg. hr. Y caps. 4,000 r. x-ray midpelvis	4 months	Vaginal hysterectomy. Bilateral salpingo- oophorectomy	Necrotic patch, 6 mm. thick, in lining of body of uterus. Multiple leiomyomas of uterus of moderate size. Adenomyosis of myometrium. Radiation changes. No malignant tumor microscopically	Living and free of detectable disease, 18 mo.
P. G. 52 II	Adenocarcinoma Grade II papillary	6,000 mg. hr. Y caps. 4,000 r. x-ray midpelvis	5 months	Vaginal hysterectomy. Bilateral salpingo- oophorectomy	Necrotic plaque 8 mm. in diameter and 5 mm. thick in lining of uterus at internal os. Necrotic polypoid mass in fundus $1.1 \times 0.8 \times 0.4$ cm. Radiation changes. No malignant tumor microscopically	Living and free of detectable disease, 14 mo.
R. B. 46 III	Adenocarcinoma Grade III	3,000 mg. hr. straight caps. 4,000 r. x-ray midpelvis	3 months	Panhysterectomy. Previous salpingo- oophorectomy	Necrotic plaque in body projecting slightly into uterine cavity and extending just below internal os. Adjacent 3 mm. of myometrium necrotic. Small leiomyoma of uterus. Chronic cervicitis. Radiation changes. No malignant tumor microscopically	Living and free of detectable disease, 2 yr. 9 mo.

were sectioned longitudinally at right angles to the mucosal lining so that practically the entire lining of the cervix and of the body of the uterus was included in blocks varying in thickness from 3 to 5 mm. The blocks in all of the four cases included the entire thickness of the wall of the cervix and of the wall of the body near the internal os. In two of the uteri, the entire thickness of the wall of the rest of the body was included in the appropriate blocks; in the other two, only the internal 1.5 to 1.8 mm. of the myometrium were included. The number of blocks obtained from any one of the uteri was not less than 27 nor more than 35. One section was taken from the surface of each block; then each block was cut halfway through and another section taken. Since the original blocks were 3 to 5 mm. thick, the net result was sections of the lining of the uterus and of the adjacent tissues at 1.5 to 2.5 mm. intervals and the total number of microscope slides prepared from any one of these 4 uteri not less than 54 nor more than 70. The tissues were stained with hematoxylin and eosin. For the purposes of this paper, our attention was centered on the exclusion, as far as possible, of any viable tumor in these uteri. An examination of the additional slides prepared from these uteri substantiated the impression gained from the study of the routine sections. No viable tumor was demonstrable. A more detailed report on the gross and microscopic findings in these uteri is being prepared. Only routine sections of uteri which showed carcinoma after irradiation were made. Similar studies have been made by Arneson,¹ Donovan and Warren,⁴ and Healey and Brown,⁷ but in each instance the dosage of radium was much less than in our series. Phaneuf¹² has shown that the minimum lethal dose for corpus cancer is from five to ten skin erythema units.

Discussion

Table I summarizes the five cases adequately treated in which no carcinoma was found in the removed uteri. Case 2 received but 2,000 mg. hours of radium in the Y applicator. Further radium was not used because of the intense cystitis and proctitis that developed. Whenever the patient develops such a reaction, the dose of radium must be decreased as permanent injury to the bladder or bowel may result. The vagina of these patients is tightly packed while the radium is in place and the bladder kept empty with a retention catheter. An enema should be given routinely before inserting the applicator so as to keep the recto-sigmoid empty and as far away from the uterus as possible. In this entire group of cases but one suffered a permanent injury due to the irradiation. This patient (Case 2, Table IV), before entering Mercy Hospital, received in a single dose 6,000 mg. hours of radium in a straight two mm. capsule. Although living, she now has a rectouterine fistula. A capsule of radium left in one position for this single dosage will over-irradiate the tissues in direct contact with the capsule. Patient in Case 5 received but 3,000 mg. hours of radium at Mercy. She had had 1,200 r. of 200 kilovolt x-ray to the skin immediately before admission, and again the reaction was too intense for further radium therapy. The combined dose, however, was considered adequate. In each of the uteri studied, necrosis of the myometrium was demonstrated to variable depths but not over 5 mm. The further radiation changes in the myometrium have been studied and form the basis of another report.

Table II summarizes the six cases inadequately treated in our opinion, and in each instance active carcinoma was still present in the removed uteri. Of interest is the finding of radiation change in the tumor of

those cases treated with x-ray alone. This demonstrates that external irradiation is of value in the treatment of the primary lesion as well as for its effect on the pelvic cellular tissues and lymphatics. The clinical grouping shows the cases to be almost equally divided into Groups II and III, and the pathologic grading is likewise evenly divided in Grades II and III. Three of the cases found free of disease were in clinical Group II and Grade II carcinomas. One was in Group III and Grade III. The only case to die to date was also in Group III and a Grade III carcinoma. This patient (Case 1, Table II), remained free of symptoms for three years. Then she received a second course of high voltage x-ray therapy and was operated upon. Active disease was found throughout the myometrium, and the patient died three months after operation from metastases to the bowel and liver.

The 11 patients operated upon, after this extensive therapy, presented no increased technical difficulty in performing the surgery. There was no immediate surgical mortality, and only one patient was morbid, this being due to an acute cystitis on the basis of the previous irradiation. At least three months should elapse between the irradiation and the removal of the uterus. This permits recovery of the tissues from the radiation effect and gives the patient an opportunity to recover from the anemia and weakness which result from this type of therapy. There is no need to fear the loss of valuable time in employing this procedure, as mentioned by Ward.¹⁷ A carcinoma so extensively irradiated if not destroyed will probably be inactive for this period of time.

Table III summarizes the 7 cases adequately irradiated but not hysterectomized. Four of these cases were curetted from one to three months after irradiation, and no malignant cells were found. Case 5, however, died one year later of peritoneal metastases. This demonstrates that myometrial or lymphatic invasion may be present, and curettage would not detect its presence, an observation stressed by Scheffey and Thudium.¹⁴ There is always the possibility that a case may be more extensive than clinical findings indicate. Elton, in studying 50 removed uteri, concluded "that hysterectomy is obviously necessary for adequate evaluation of the factor of invasion." Whether removal of the uterus in this case would have prevented progression of the tumor is speculation.

Table IV groups the cases inadequately treated in our opinion and not hysterectomized. Three of the six patients who were curetted still had active disease. This group of cases were mostly in clinical Group III, two being in Group II, and one in Group IV. The survival periods definitely demonstrate the value of palliative irradiation in the inoperable group, while the end results demonstrate that clinical Group I and II carcinomas carry the highest curability rate irrespective of the grade of carcinoma.

Table V completes this group of 20 cases diagnosed at our clinic and irradiated but not operated. Cases 3 and 4 had adequate radium therapy but no x-ray. One patient in clinical Group II survived six years when she died of heart disease, while the other patient in Group II died three years later of carcinoma. The two remaining patients received palliative irradiation only.

Table VI showing the cases not verified pathologically at Mercy Hospital but referred by dependable physicians as adenocarcinomas demonstrates that the patients treated with x-ray and radium according to our technique have a higher survival rate. In Case 4, although no tissue could be obtained on curettage, the extension outside the uterus progressed rapidly.

TABLE II. SUMMARY OF CASES RECEIVING PREOPERATIVE RADIATION THERAPY

PATIENT AGE GROUP	DIAGNOSIS ON CURETTINGS	RADIUM AND X-RAY	INTERVAL BETWEEN RADIATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
E. D. 70 III	Adenocarcinoma Grade III	4,500 mg. hr., straight caps. 4,000 r. x-ray mid- pelvis	3 years	Vaginal hysterectomy Bilateral salpingo- oophorectomy	Adenocarcinoma of endometrium with diffuse invasion of myometrium. Multiple leiomyomas of uterus. Marked radiation changes with absence of much of cervix	Died 3 mo. after operation of metastases
A. L. 42 III	Adenocarcinoma Grade II Areas of squamous metaplasia (adenocanthoma)	2,000 r. x-ray mid-pelvis 1,500 r. x-ray mid-pelvis	2 months	Panhysterectomy Bilateral salpingo- oophorectomy	Large adenocanthomatous ulcer in body extending slightly below internal os. Deep invasion of myometrium. Metastases to anterior lip of cervix and left ovary	No follow-up after 11 mo.
A. V. 70 III	Adenocarcinoma Grade III	4,000 r. x-ray mid-pelvis No radium	8 months	Panhysterectomy Bilateral salpingo- oophorectomy	Polypoid adenocarcinoma $2.5 \times 2.5 \times 1$ cm. in fundus. Invasion of adjacent myometrium. Multiple small leiomyomas. Chronic salpingitis	Living and free of detectable disease, 6 yr.
M. M. 61 II	Adenocarcinoma Grade III	4,000 r. x-ray mid-pelvis No radium Pyometra	3 months	Vaginal hysterectomy Bilateral salpingo- oophorectomy	Adenocarcinomatous ulcer in upper cervical canal. Extension into adjacent coats of cervix and adjacent myometrium. Chronic cervicitis. Radiation changes	Living and free of detectable disease, 14 mo.
T. T. 48 II	Adenocarcinoma Grade III	3,500 mg. hr., straight caps. No x-ray	1 month	Panhysterectomy Bilateral salpingo- oophorectomy	Adenocarcinoma of endometrium with deep invasion of myometrium. Radiation changes	Living and free of detectable disease, 2 mo.
A. M. 42 II	Adenocarcinoma Grade II	1,800 mg. hr., straight caps.	4 weeks	Panhysterectomy Bilateral salpingo- oophorectomy	Necrotic mucosal elevation 4 mm. in diameter in body near internal os. Elsewhere adenocarcinoma confined to endometrium. Radiation changes. Chronic cervicitis. Left tuboovarian abscess	Living and free of detectable disease, 4 yr. 4 mo.

TABLE IV. SUMMARY OF CASES RADIATED BUT UTERUS NOT REMOVED
(Cases having inadequate x-ray and radium)

PATIENT AGE GROUP	DIAGNOSIS ON CUTTINGS	RADIUM AND X-RAY	INTERVAL BE- TWEEN RADI- ATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
A. S. 62 Group III	Adenocarcinoma Grade III Adenocanthoma	4,200 mg. hr. Ra.El. Y-cap. 4,000 r. x-ray midpelvis	2 months	Dilatation and cu- rettage	Very little tissue ob- tained. Necrotic tis- sue. No carcinoma	Living 5 years
M. M. E. 70 Group III	Adenocarcinoma Grade III	6,000 mg. hr. Ra.El. in st. cap. 1 sitting 4,000 r. x-ray	3 months	Dilatation and cu- rettage	No tissue obtained	Living 4 yr. Recto- vaginal fistula
E. S. 65 Group III	Adenocarcinoma Grade III with areas of squa- mous metaplasia (adenocanthoma)	4,100 mg. hr. Ra.El. Y-cap. 4,000 r. x-ray midpelvis		None	None	Lived 5 yr. Developed abdominal mass
E. L. 48 Group II	Adenocarcinoma Grade III Adenocanthoma	3,850 mg. hr. Ra.El. in tubes before admission 2,000 r. x-ray midpelvis	5 months 10 months	Dilatation and cu- rettage Dilatation and cu- rettage	Rapidly growing ad- enocanthoma	Lived 2 years
E. J. E. 68 Group III	Adenocarcinoma Grade III areas of squa- mous metaplasia (adenocanthoma)	Radium 2 yr. and 1 yr. be- fore admission, 6,720 in Y- cap. 4,000 r. x-ray with 200 K.V.	8 months	Dilatation and cu- rettage	Pyometra Adenocarcinoma, Grade III	Lived 1 year
E. T. 73 Group III	Adenocarcinoma Grade III	3,120 mg. hr. Ra.El., Y cap. 4,000 r. x-ray midpelvis	5 months	Dilatation and cu- rettage	No tissue obtained	Living 3 yr. 4 mo. free of detectable disease
A. F. 66 Group IV	Adenocarcinoma Grade II Papillary	3,000 mg. hr. straight cap. 4,000 r. x-ray midpelvis, re- peated	None	None	None	Living 4 yr. 3 mo. with active disease
A. G. 53 Group II	Adenocarcinoma Grade II Papillary	4,100 mg. hr. Ra.El., Y-cap. 1,000 r. x-ray midpelvis	None	None	None	Did not finish therapy
A. M. 57 Group III	Adenocarcinoma Grade II	2,160 mg. hr. Ra.El., Y-cap. 4,000 r. x-ray midpelvis	3 months 5 months 1 year	Dilatation and cu- rettage Dilatation and cu- rettage Dilatation and cu- rettage	Adenocarcinoma No evidence of carci- noma No evidence of carci- noma	Living 2 years and 2 months

TABLE III. SUMMARY OF CASES RADIATED BUT UTERUS NOT REMOVED
(Cases having adequate x-ray and radium)

PATIENT AGE GROUP	DIAGNOSIS ON CURETTINGS	RADIUM AND X-RAY	INTERVAL BE- TWEEN RADI- ATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
L. C. 41 Group II	Adenocarcinoma Grade III	6,900 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	2 months	Dilatation and cu- rettage	Necrotic endometrium No evidence of malignancy	Well and free of de- tectable disease 12 yr.
L. W. 71 Group II	Adenocarcinoma Grade II Papillary	6,780 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis		None	None	Living and well 6 yr. 5 mo.
E. F. 41 Group II	Adenocarcinoma Grade II Papillary	5,940 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	3 months	Dilatation and cu- rettage	No evidence of car- cinoma	Living 2 yr. Free of detectable disease
G. M. 56 Group II	Adenocarcinoma Grade II	6,000 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	None	None	None	Living 8 mo. Had early adenocarcinomatous changes polyp, 1939
M. O. 73 Group II	Adenocarcinoma Grade III	6,000 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	3 months	Dilatation and cu- rettage	No tissue	Died one yr. later of peritoneal metastases
C. M. 64 Group III	Adenocarcinoma Grade II with areas of squa- mous metaplasia (adenocanthoma)	6,880 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis		None	None	No follow-up.
T. R. 55 Group II	Adenocarcinoma Grade II	5,640 mg. hr. Ra. in Y-cap. 4,000 r. x-ray midpelvis	1 month	Dilatation and cu- rettage	Radiation changes in epithelium. No defi- nite carcinoma cells noted	Living 2 yr. 8 mo. Free of detectable disease

TABLE VI. CASES NOT VERIFIED PATHOLOGICALLY AT MERCY BUT REFERRED BY DEPENDABLE PHYSICIANS AS ADENOCARCINOMAS

PATIENT AGE GROUP	DIAGNOSIS ON CURETTINGS	RADIUM AND X-RAY	INTERVAL BETWEEN RADIATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
R. B. 60 Group III	Adenocarcinoma	6,000 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	None	None	None	Living 10 yr. No detectable disease at this time
A. M. 58 Group III	Adenocarcinoma	6,000 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	1 year	Dilatation and curettage	Hyaline degeneration, no carcinoma	Living 4 yr. 6 mo. No detectable disease
D. M. 65 Group II	Adenocarcinoma	6,000 mg. hr. Ra.El. in Y-cap. 4,000 r. x-ray midpelvis	2 weeks	Dilatation and curettage	No evidence of carcinoma	Living 18 mo. No detectable disease
M. G. 68 Group IV	Adenocarcinoma	6,000 mg. hr. st. cap. 1 sitting before admission to Mercy 4,000 r. x-ray midpelvis	4 months	Dilatation and curettage	No carcinoma	Died 7 mo. after x-ray therapy
Sr. M. E. 55 Group III	Adenocarcinoma	2,880 mg. hr. Ra.El. in Y-cap. 9 mo. prev. 2,400 4,000 r. x-ray midpelvis	1 year	Dilatation and curettage	No tissue	Died of metastases 4 years later
M. S. 72 Group III	Adenocarcinoma	2,520 mg. hr. Y-capsule 4,000 r. x-ray midpelvis	None	Dilatation and curettage 11 mo. previous 8 x-ray R's	Adenocarcinoma	Died of metastases 2 yr. 2 mo. after therapy
Sr. M. A. 58 Group II	Adenocarcinoma	1,300 mg. hr. 4,000 r. x-ray midpelvis	6 weeks	Total abdominal hysterectomy Bilateral salpingo-oophorectomy	Adenocarcinoma	Living 7 yr. No detectable disease at this time

TABLE V. SUMMARY OF CASES RADIATED BUT UTERUS NOT REMOVED
(Cases having incomplete treatment)

PATIENT AGE GROUP	DIAGNOSIS ON CURETTINGS	RADIUM AND X-RAY	INTERVAL BETWEEN RADIATION AND OPERATION	OPERATION	LABORATORY REPORT	RESULT
R. G. 72 Group III	Adenocarcinoma Grade II	2,400 mg. hr. Ra.El. in Y-cap. 1,500 r. x-ray midpelvis		None	None	Diabetic, stopped therapy
C. B. 67 Group IV	Adenocarcinoma Grade IV	No radium 1,600 r. x-ray midpelvis		None	None	Palliative x-ray. Lived 2 months
A. C. 57 Group II	Adenocarcinoma Grade III	7,200 mg. hr. Ra.El. in Y-cap. No x-ray		None	None	Died 6 yr. later of coronary heart disease
H. D. 56 Group II	Adenocarcinoma Grade III	6,000 mg. hr. Ra.El. in Y-cap. No x-ray		None	None	Died 3 yr. later

Discussion

DR. HENRY L. DARNER, WASHINGTON, D. C. (By Invitation).—We have not found it possible to divide these patients into the four clinical groups suggested by the authors. The size of the uterus, the presence of any variation in consistency of the wall of the fundus and the variable degrees or complete absence of parametrial invasion have been our principal classifying factors on examination.

In our experience a tandem application, with a tube 6 cm. in length, containing 100 mg. of radium, with a wall thickness of 1 mm. gold or platinum and rubber, permitted to remain in the uterus for forty-eight hours, has usually so modified adenocarcinoma of the fundus that it cannot be recognized macroscopically or microscopically by the pathologist upon removal of the uterus, six weeks to three months after radiation. The usual exceptions are in cases where the primary site of the lesion is the apex of the fundus or where there is already myometrial or parametrial invasion.

Sterilization of epidermoid cancer of the cervix by external radiation requires from 10,000 to 18,000 r. directed over four to six ports in women under 150 pounds in weight. Above this weight external radiation is futile. Adenocarcinoma is, of course, much more resistant to radiation. Adequate irradiation of the fundus in the usual corpulent postmenopausal patient by external roentgen therapy is a most difficult problem and impossible in the average case.

The purpose of radiation therapy in the case which is amenable to hysterectomy is to sterilize the more radiosensitive elements of the tumor. This has been accomplished in our hands by intrauterine radium therapy without damage to the urinary bladder or intestines, either or both of which can be seriously affected by external roentgen therapy intensive enough to be theoretically and practically cancericidal to fundal malignancy. Fibrosclerosis of the rectum and sigmoid with attendant intractable diarrhea or more serious permanent injury and chronic irritative lesions of the bladder are frequent complications of intensive, external, roentgen therapy.

We have not found the postradiation curettage reliable as an effective means of early recognition of recurrence or failure of radiation therapy. We have all had the experience of patients with no conceivable evidence of local residual or recurrent pathology whose first evidence of recurrence is massive remote metastases.

The increased constitutional and local effects, at least in the overnourished individual, which so frequently follow adequate, external radiation will probably lead to further controversy between those who favor preoperative therapy and those who do not. We reserve intensive, external radiation for the cases in which the original and postradiation study of the patient have definitely proved persistent parametrial involvement and made postradiation hysterectomy impossible.

DR. LEWIS F. SMEAD, TOLEDO, OHIO.—I am in full accord with the recent trend toward more thorough preoperative radiation of adenocarcinoma of the uterus. All operable cases, physically fit to withstand surgery, should receive adequate preoperative radiation by x-ray or radium or by both. The best results so far obtained have been secured by this method. One might make an occasional exception in an early case, histologically classified as in Grade I or II and treat it by surgery alone or by surgery and postoperative radiation. Other exceptions might be made with operable cases classified as Grade IV or as embryonal types of carcinoma. It may be best to treat these cases by radiation alone. It is not well, however, to put too much faith in histologic classifications.

One is reminded that this subject of radiation treatment is an ever changing one when one learns that the well-established method of preoperative radiation of carcinoma of the breast recently has been discontinued in some institutions, among them the Memorial Hospital in New York. It has been discontinued because it

If we now group all the cases adequately treated according to our standard, they number 15 of the 38 cases. These cases will be followed to determine their five-year curability rate. In the future all cases will be operated upon following the course of irradiation therapy as outlined. For, as Masson and Gregg¹⁰ have stated, "Whether pre-operative irradiation combined with operation gives better results than operation alone will require many years to prove."

Summary

1. The technique is given for the treatment of carcinoma of the uterine fundus by combined x-ray and radium therapy, as employed at the Mery Hospital Institute of Radiation Therapy.

2. A group of 77 proved cases of adenocarcinoma have been divided into those receiving preoperative and postoperative irradiation. The patients receiving preoperative radiation therapy are grouped clinically and graded microscopically.

3. Eleven patients receiving preoperative irradiation were hysterectomized. Five of the uteri adequately treated according to our method were free of carcinoma. Serial blocks of four of these five uteri failed to reveal residual carcinoma. The remaining 6 patients considered as inadequately treated all had active carcinoma remaining in the uterus.

4. The 27 remaining cases, irradiated but not hysterectomized, add further evidence as demonstrated by curettage or follow-up that adequate irradiation in clinical Group I or II carcinomas of the fundus has a definite value.

5. Although we cannot advocate this treatment as a substitute for surgery in patients who are good surgical risks, we feel that our plan of preoperative irradiation should be carried on until sufficient case records are on hand to determine whether the five-year salvage is greater than in cases treated by surgery and postoperative irradiation.

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Many reports are appearing in the literature at the present time of uteri studied after inadequate amounts of irradiation. Other investigators used from 2,000 to 3,500 mg. hours of radium in the uterine cavity and removed the uterus before a two weeks' interval. We know that the irradiation effect has not reached its maximum so quickly and therefore these studies are valueless. I do not believe that delaying the operation is a factor in recurrence if the carcinoma is thoroughly irradiated.

Replying to Dr. Calkin's question, I believe earlier impressions of the sensitivity of adenocarcinoma came from the fact that we had so few adenocarcinomas of the cervix. It was, of course, the opinion of most gynecologists and pathologists that the adenocarcinomas were more resistant than the squamous cell carcinomas. I now believe, if we had the same number of cases it would be found that the relative resistance would be about the same.

As to Dr. Pendleton's question, I do not believe that irradiation causes any disturbance of the capillary bed. I encountered no difficulty in the surgery, and there was no immediate surgical mortality and only one case with fever.

RADIUM THERAPY IN BENIGN UTERINE BLEEDING*

A Study Based on 350 Cases

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THE clinical study and the analysis of the results obtained in this comparatively large series of cases differs measurably from the methods commonly employed in the evaluation of the efficiency of a therapeutic agent in the treatment of disease. Ordinarily studies of a large series of cases, emanating from clinics, represent the work of a number of surgeons in both private and ward patients. The symptoms, objective and subjective, are recorded by junior members of the staff. The selection of a given procedure represents the judgment of many surgeons or frequently a standardized method of treatment. The subsequent history and final results are collated and tabulated by members of the staff, who often do not have an intimate knowledge of the medical status of the patient from the inception to the termination of the treatment.

This series of cases, covering a period of fourteen years, consists of private patients, who sought medical advice because they suffered from vaginal bleeding and associated symptoms. Each patient was first seen in the office. The medical history, the physical examination, the indication for the use of radium, the postoperative course, morbidity and complications, the subsequent history, and the final results were evaluated and carefully recorded on the history cards by the senior author.

The junior author tabulated all the facts from the records. The data obtained truly mirror the usefulness of and may serve as criteria for

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delayed the operation three or four months, and because it resulted in poor wound healing and other complications. I am fully aware that these same faults may be found with preoperative radiation of carcinoma of the body of the uterus.

The x-ray factors employed in the treatment of my cases of carcinoma of the uterus, and furnished me by my associates in the x-ray department, are a 400 kv. constant potential current operating a sealed x-ray tube at 5 milliamperes, a filter equivalent of 3.0 mm. of copper, a focal skin distance of 65 cm., a field size of from 250 to 400 square cm., and H.V.L. of 4.0 mm. of copper. The output is 35 r. without backscatter and 42 r. with backscatter. The depth dose at 10 cm. is nearly 50 per cent on fields above 250 square cm. Four pelvic ports are used of 250 square cm. or more in size. In a pelvis measuring 20 cm. in anteroposterior diameter the dose delivered to each port is about 2,800 r. or 11,200 r. total, measured with backscatter. This delivers about 40 per cent to the midpelvis or 4,800 r. to the tumor area. About 360 r. with backscatter are delivered to one port each day. The dose is delivered in a total of 32 daily treatments.

About two weeks after the last x-ray treatment the radium treatments are carried out. From 3,600 to 4,000 mg. hr. are given within the uterine cavity in multiple capsules filtered by 1.5 mm. platinum, and 1,600 to 2,000 mg. hr. with the same filtration plus 1 cm. of sponge rubber are applied against the cervix and vaginal vault. The latter is intended to take care of any malignancy in the cervix or vagina and to add to the general pelvic dose. The treatments are given rather slowly in two doses over a period of from eighty-nine to ninety-nine hours using only 80 mg. of radium element with heavy filtration. There is an interval of 24 hours between the two doses. The patients are usually ready for hysterectomy in from six to eight weeks after the last radium treatment.

It is felt that this method of treatment should deliver an adequate dose to the uterus and pelvis. There has not been time to check over the reports on the uteri removed at operation, but most of them have shown no remaining carcinoma on routine gross and microscopic examination. I have not found that this amount of treatment has made the hysterectomy difficult or caused poor wound healing.

DR. LEROY A. CALKINS, KANSAS CITY, KAN.—For a number of years we have proceeded on the general rule that an adenocarcinoma, whether of the body of the uterus or the cervix, required approximately twice the radiation dosage to be lethal as was required for a squamous cell carcinoma of the same size and location. Dr. Healy has recently cast doubt on this difference in susceptibility. I wonder whether Dr. Schmitz has gone far enough to be able to tell us the relative radiosensitivity of the squamous cell carcinoma and the adenocarcinoma.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—Assuming that you have given proper intrauterine dosage and the proper roentgen crossfire through various ports are you not very much worried about the loss of the capillary bed in the parametrium after three months?

DR. SCHMITZ (closing).—It is admittedly very difficult to control the position of radium in the uterus. If you place capsules in series in a rubber tube and then pack them into the uterine cavity there is no way of telling whether they shift, nor can you determine the exact dosage you are giving at any one point. That is why the Y applicator was adopted. We are giving from 7.5 to 8 erythema doses in the uterus, which we believe is necessary to destroy the average carcinoma.

As to Dr. Smead's remark about preoperative x-ray irradiation, I believe that it has a definite place in the treatment of uterine carcinoma. I am not advocating this method of treatment for adenocarcinomas of the uterus, but I want to continue the study to evaluate this method so when forced to use irradiation on a poor operative risk, we will know which method of irradiation will give the best results.

of curing the symptoms but also as to the safety of the procedure. In the light of accumulated experience, to remove a uterus, with or without a fibroid, when a cure can be accomplished by a therapeutic agent, less dangerous and just as effective, seems not to be a rational procedure. There certainly is no justification for subjecting a middle aged woman, who is suffering from idiopathic uterine bleeding, to a major surgical operation.

We are convinced, as a result of this study, that radium is the only logical therapeutic agent in all cases of uterine bleeding not complicated by fibroids or malignancy, in women in whom childbearing is no longer a problem. Sixty-five patients in this series belong in that category and a complete cure was accomplished in all.

Uterine Bleeding Associated With Fibroids

This class of cases require greater clinical acumen correctly to decide as to the proper method of treatment. The size of the uterus, the location of the fibroids, the sensitivity of the tumor, the pain it induces, associated organic diseases, obesity, the operative risk, the sexual history of the patient, as well as the husband, should be taken into consideration before treatment is instituted.

In this series of cases complete involution of the tumor took place in 232 patients. These results definitely demonstrate the usefulness of radium in properly selected cases.

Patients suffering from submucous, pedunculated, and broad ligament fibroids, whether small or large, are never proper subjects for radium therapy. Necrosis and infection of submucous fibroids often follow radiation. When a tumor projects into the uterine cavity it is easily elicited by the curette; the uterine surface is uneven, causing a zig-zagging of the curette in its up and downward movements.

Radium is definitely contraindicated in all cases of uterine bleeding in patients who give a history of having a pelvic infection or in whom pelvic adhesions may be suspected because of a previous abdominal operation. It should not be used in patients suffering from fibroids when they cause much pain and tenderness. The pain is usually caused by trophic disturbance in the tumor, which is likely to be aggravated by the radiation. The bleeding may cease but the pain remains a troublesome and annoying symptom.

Uterine Bleeding Associated With Essential Hypertension

There is a prevailing opinion among clinicians that hypertension is a contraindication for and adds to the risk of an abdominal hysterectomy. Our experience differs in this respect. Patients suffering from essential hypertension, not accompanied by myocardial disease or obesity, hardly assume an immediate additional risk in undergoing a major pelvic operation. Convalescence is seldom complicated by the hypertension; furthermore they are less subject to emboli. However, the sudden in-

the application of radium in benign uterine bleeding. The conclusions arrived at represent an objective estimate of the effectiveness of radium for the control of bleeding in properly selected cases.

The symptoms that primarily impel these patients to seek medical advice are: (1) abnormal vaginal bleeding, (2) pain in the lower portion of the abdomen, and (3) pressure in the pelvic region. The cardinal symptom, however, is the profuse or irregular vaginal bleeding which may or may not be accompanied by pain or pressure, disturbed micturition, or other symptoms. The nature and complexity of the symptoms these patients present do not as a rule lend themselves to a standardized form of treatment. The pelvic findings, the marital and social status, the general constitution of the patient should form an all inclusive medical picture which would bespeak either for conservative or radical procedures for the control and cure of the symptoms.

The pathology underlying the disturbed vascularization of the endometrium requires further elaboration and clarification. Even microscopic study of the endometrial tissue often does not help to clarify the pathologic process, for in this series of cases a resting endometrium was found in 112, or 39.3 per cent, and a hyperplastic endometrium in 130, or 45.6 per cent, of the patients. Obviously it is difficult to explain bleeding in the presence of resting endometrium, or the existence of an endocrine imbalance without causing some changes in the endometrium. Furthermore, how does a simple curettage, which often cures the bleeding, correct an endocrine imbalance? These are puzzling problems to the clinician which require further investigation.

It is superfluous to state that no treatment of any kind should be instituted in cases of uterine bleeding before a microscopic study is made of the endometrium. It may be mere coincidence that in twelve patients in this series corpus carcinoma was discovered only after the curettings were examined. In none of these patients was malignancy suspected nor had they given symptoms which would warrant the diagnosis.

The crux of the problem in the treatment of uterine bleeding with or without fibroids is: What type of case should have the offending organ removed or when should radium be used to control the symptoms? Theoretically this should not be difficult for clinicians who are not delimited in their approach to this problem by one particular method of treatment.

The indications and contraindications for radium therapy in uterine fibroids, as enunciated by Ward,¹ will prove satisfactory in the average case. However, one is perplexed by this statement that "surgery is indicated in bleeding myomatous uteri as a general rule."

Though it is generally agreed that radium therapy is contraindicated when the uterus is enlarged to the size of more than a three months' pregnancy, actually there is no theoretical line of demarkation. The clinical findings must be evaluated in each patient, not only from the standpoint

often aggravates the relaxation of the vaginal vault and not infrequently leads to its complete eversion, a most troublesome complication and extremely difficult to repair. Again, vaginal hysterectomy without reconstruction of the pelvic floor is definitely an incomplete surgical procedure. Until recently, for some reason, repair of the vaginal vault was seldom undertaken together with intrauterine radiation. It was believed that the healing power of the repaired structures would be affected by the rays. Clinical experience disproved this hypothesis. The healing process is not at all interfered with by the presence of radium in the uterus. In this series 65 patients had plastic operations on the cervix and vaginal vault. In seven the interposition operation was performed. Neither the morbidity was increased nor was the stay in the hospital prolonged. The application of radium in conjunction with repair of the vaginal vault in this group of patients proved more satisfactory than any other surgical procedure we had used heretofore in this class of cases. We believe it to be the method of choice and that it will in the future supplant other surgical procedures. Neither vaginal nor abdominal hysterectomy compares with it favorably.

It is anomalous that radium therapy is extensively practiced by radiologists. They are neither technically trained to deal with surgical procedures nor have they the necessary knowledge to evaluate properly the clinical condition of the patient. The indications and contraindications for curettage and radiation are gynecologic problems; especially is this true of patients who require supplemental surgical procedures.

We desire to emphasize briefly some of the more important items dealing with the management and results obtained in this series of cases.

Dosage

When we first instituted radium therapy in the treatment of these patients we varied the dosage from time to time and finally came to the conclusion that 1,800 mc. hr. is the appropriate dose for women aged 40 years or older. The ideal method is to insert 25 mg. in the uterus, to be left seventy-two hours, the patient thus receiving 1,800 mc. hr. of radium. Nausea and radium burns are less likely to occur when a smaller dose of radium is used over a greater number of hours.

Morbidity

Occasionally the patient will complain of crampy pain in the lower portion of the abdomen induced by the foreign body in the uterus. In 314, or 89 per cent of cases, there was no postoperative reaction. Included in these are 50 patients who had supplemental repair of the vaginal vault. Thirty-six, or 10.3 per cent, including 15 patients, who had vaginal plastics, had morbidity lasting from three to seven days. With the exception of one patient their stay in the hospital was not prolonged.

duction of menopause is likely to increase further the blood pressure. Therefore it is not advisable to use radium in these patients, because of its acute effect on ovarian function, but instead perform hysterectomy without removing the ovaries, so that the patient will have the benefit of some ovarian function for one or two years.

A decision in favor of radium therapy often has to be made on the basis of the psychology underlying the sex life of the husband. Many of the husbands have reached a period of instability of their sexual powers; they are less disturbed mentally when they know that a cure can be accomplished without actually removing the genital structures, thus eliminating their apprehension that a woman who has the genital organs removed is no longer fit for sexual relationship. The average woman, too, welcomes a therapeutic measure which does not entail the removal of the uterus. She may display some anxiety about the cessation of menstruation, but she finds solace in the fact that her genital organs will remain intact. This is especially true of men and women who suffer from some imbalance of the nervous system. In this regard our experience differs from that of Flynn,² who maintains that highly neurotic and oversexed individuals are not suitable patients for radiation therapy. On the contrary, it has been our observation that the neurotic patient takes more kindly to a cure that can be accomplished by radium instead of hysterectomy.

Patients nearing menopause, who suffer from polyps of the cervix, form a special group for radium therapy. Usually hyperplasia of the endometrium is associated with polypoid cervical growths. These patients seldom bleed profusely, but spot and stain irregularly. The removal of the polyp should be followed by curettage, especially if the pedicle is situated high in the cervical canal. The application of a small dose of radium in these cases will not only cure the spotting and staining but will prevent future polypoid formation. The cessation of menstruation does not disturb these patients; on the contrary, they welcome it, for they no longer have to be anxious about pregnancy or resort to contraceptive measures.

The immediate constitutional reaction of intrauterine radiation is also not fully understood. The nausea, mild and severe, the flushes that often develop within forty-eight hours after the insertion of radium, can be induced only through the blood and lymphatic streams. Flushes occur because the estrogenic output is reduced. The degree of nausea usually depends upon the severity of the acidosis. How can these disturbances take place so rapidly unless the body fluids are directly affected by the radium?

Uterine Bleeding Associated With Pelvic Lacerations

Many patients who suffer from uterine bleeding require pelvic repair. Abdominal hysterectomy, without repairing the lacerated structures,

interesting to note that not a single patient developed involutional melancholia during the menopausal period, though we have observed a number of such instances following hysterectomy and bilateral oophorectomy.

Involution of the Fibroid Tumor

In 232 patients, or 81.4 per cent, complete involution of the mass occurred, partial in 48, or 16.8 per cent. In a number of patients the uterus atrophied to a subnormal size. In the majority of cases hardly a trace of the fibroid could be elicited by clinical examination after eighteen months. Corseaden⁵ observed "a complete disappearance of the mass in 55.8 per cent, in 28 per cent a reduction of 50 per cent or more, in 12.5 per cent a definite and important reduction."

Postradiation Pain

Many patients complained of localized pain in the lower part of the abdomen or the groins during the involutional process of the fibroid. The pain diminished and gradually subsided when the fibroid had completely or partly involuted. Clinically it is difficult to interpret the symptom of pain in the pelvic region in multiparous patients, and it is not easy to differentiate it from the specific pain induced by the involution of the fibroid. However, if upon examination the uterus is found to be sensitive or a tender spot is elicited in the region of the fibroid, it is safe to assume that the local pain is caused by the circulatory disturbance within the fibroid.

Number of Periods Following Radiation

In 197, or 56.3 per cent, the menstrual function disappeared immediately. Sixty-eight, or 19.4 per cent, menstruated once. Eighty-five, or 24.3 per cent, menstruated two or three times. One patient at the age of fifty began to menstruate regularly after a complete cessation of menstruation induced by radium twelve years before. Another patient began to menstruate after an interval of five years; she became pregnant and aborted in the third month.

Five patients, or 1.8 per cent, failed to respond to radium therapy. They continued to bleed irregularly and at times profusely. Hysterectomy finally was performed in four of the cases. Two patients required supplemental x-ray therapy, and in two others radium therapy had to be repeated. One patient, who had two applications of radium, developed carcinoma of the cervix and body of the uterus five years later. We never observed a malignancy develop as a sequel to intrauterine radiation. In this respect our experience coincides with that of W. Neill, Jr.⁶

Conclusions

1. Uterine bleeding can be cured by curettage and intrauterine insertion of radium in properly selected cases.

Leucorrhea

There is no doubt that intrauterine radiation increases the cervical discharge temporarily in a considerable number of patients. The necrosis of the endometrium induced by the radium often forms a thick, slimy discharge, lasting about two or three weeks, and subsides as soon as the endometrial debris is completely eliminated. The discharge, however, is not more profuse than that induced by cauterization of the cervical canal performed preliminarily or in conjunction with supravaginal hysterectomy.

Rectal Bleeding

Three patients had periodic rectal bleeding, which lasted over a period of years. No lesion in the rectum or anus was discernible. It was not accompanied by pain. The patients experienced the same sensations which they usually had preceding their normal menstruation. Clinically, it could only be interpreted as vicarious menstruation; though in one patient a proctologist was strongly suspicious of the development of an early malignancy in the upper portion of the rectum, the subsequent history of the periodicity of the bleeding confirmed the diagnosis of vicarious menstruation.

Vesical Disturbance

The severity of vesical symptoms in this series of cases was largely judged by the frequency of nocturnal micturition and how often the patient was awakened by the desire to urinate. Thirty-seven, or thirteen per cent, were definitely disturbed during day and night by the frequent desire to pass urine for many weeks following the operation. Some of these patients, however, had vaginal plastics and had to be catheterized for a number of days. In our experience, extreme vesical irritation following intrauterine radiation does not occur as frequently as is generally ascribed to it.

Menopausal Symptoms

Cessation of ovarian function, whether induced by radiation or castration, is sudden and therefore the menopausal symptoms are more acute. In the last analysis, the severity of the symptoms in normal and artificial menopause largely depends upon the compensatory constitutional adjustment of the patient. Menopausal disturbances do not differ, whether induced by radiation or castration. The belief that radiation causes more pronounced symptoms is erroneous and not confirmed by careful clinical observation. Schriener³ and others have reached the same conclusion. Norris and Behney⁴ found that the menopausal symptoms following intrauterine radiation occur in only 59 per cent of the cases. In our series, 49.7 per cent had no or only mild flushes, moderate in 40.6 per cent, and severe in 3.7 per cent. It is

4. Norris and Behney: AM. J. OBST. & GYNEC. 32: 661, 1936.
5. Corseaden, J. A.: AM. J. OBST. & GYNEC. 22: 74, 1931.
6. Neill, W., Jr.: J. A. M. A. 88: 1867, 1927.

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Discussion

DR. RALPH D. CAMPBELL, MADISON, WIS.—There is no consensus of opinion as to radiation therapy in the treatment of uterine fibroids. The literature upon this subject is exhaustive, interesting and instructive, and indicates the greatest divergence of opinion as to the use of surgical methods and/or radiation therapy. Interestingly enough, in Europe radiation therapy takes precedence over surgery. In a symposium presented by the Chicago Gynecological Society upon this subject it was shown that leading gynecologists in that city were treating 95 per cent of all fibroids by surgery, leaving 5 per cent for radiation, which undoubtedly reflects the surgical tendency in the treatment of fibroids in this country.

The foregoing statements make Dr. Rongy's paper a most important one and certainly challenges the time-honored surgical treatment of fibroids. In the United States Howard A. Kelly and Curtis F. Burnam have treated thousands of cases successfully by radiation therapy to the exclusion of surgery.

Based upon a considerable experience, I can say that patients in, near, or past the menopause presenting large fibroids can be successfully treated by intrauterine radium.

Dr. Rongy has enumerated the well-known contraindications to the use of radium, such as age, anemias, pelvic inflammatory disease, submucous and subserous fibroids, hypertension, etc. However, I wish to point out that extreme anemia is not a contraindication to radiation, and this is especially true of intrauterine applications. In addition, the size of a tumor has been stressed by many observers as a contraindication to radiation. However, it is not the size that counts but whether or not it presents signs of degeneration.

I must re-emphasize that a diagnostic curettage is indicated in all cases to rule out intrauterine pathology and primarily carcinoma.

The essayist recommends 1,800 mc. hr. as the appropriate dosage continued over a period of three days, with which I cannot agree. Neither can I agree with his reasons for the extended dosage. It has been my practice to deliver a dose of 1,500 mc. hr. within the twenty-four-hour period with excellent results. My experience has shown a higher morbidity with the long continued dosage.

Dr. Rongy's observations upon morbidity, leucorrhea, bladder disturbances, menopausal symptoms, tumor involution and the menses are what one would expect.

It is interesting to note that the author has used radium placements at the time of plastic operations with excellent results, a procedure which I have been hesitant to do. It would seem to me that the procedure of choice would be a vaginal hysterectomy plus a complete repair.

I wholeheartedly endorse the statement that curettage and radium therapy should be performed by the gynecologist and not the radiologist.

At the University of Wisconsin we have used roentgen ray therapy with excellent results in the suitable age group as a sole agent in the treatment of many fibroid cases, naturally making the proper exclusions and not paying too much attention to the size when the tumor shows no signs of degeneration. It is common practice at the time of diagnostic curettage to decide upon a radium placement both from the standpoint of convenience to the operator and economy to the patient. Such a procedure is debatable in making a decision between the use of intrauterine radium and deep roentgen therapy. Then, too, such complications as extensive intrantrine

2. In 285 patients, the bleeding was accompanied by fibroids; in 65, no fibroids were present.

3. The average dose required to induce artificial menopause is 1,800 me. hr. A small dose of radium is preferable to a concentrated dose.

4. Complete involution of the tumor took place in 81.4 per cent, partial involution in 16.8 per cent; not affected by the radium, 5 patients.

5. It is not advisable to use radium in patients who suffer from essential hypertension and who have no other contraindication for operation.

6. Radium is contraindicated in cases in which the uterus is enlarged to more than fourteen weeks' pregnancy. It should not be used when a submucous fibroid is suspected, nor is its use advisable in subperitoneal or broad ligament fibroids.

7. It is dangerous to use radium in patients who give a history of having had a pelvic infection.

8. The menopausal syndrome is not accentuated by radium.

9. The leucorrheal discharge is increased for a period of six to seven weeks in a goodly number of cases.

10. Sexual relationship is less likely to be disturbed following the use of radium. The libido is definitely not affected.

11. Curettage and intrauterine radiation can be safely utilized in at least 35 per cent of patients suffering from uterine bleeding. It should replace abdominal hysterectomy in 25 per cent of cases and vaginal hysterectomy in 40 per cent.

12. Curettage and radium therapy should be performed by gynecologists, not by radiologists.

The results obtained in this and other series of cases definitely show the advance made in the practice of gynecology. Broadly conceived, surgery is but an admission of the shortcomings of medical science. The greater the progress of the science of medicine, the less there will be need for surgical intervention. This is best illustrated by the therapeutic value of the recently discovered sulfa drugs. Operative procedures of the middle ear, mastoid, or empyema of the chest have been greatly reduced by their use. Similarly, intrauterine radiation, used in properly indicated cases, will reduce the operative incidence in patients suffering from uterine bleeding, with or without fibroids, in about 35 per cent of cases. A therapeutic agent which will help to reduce the morbidity and mortality in any pathologic lesion must not be ignored and should be made a part of the medical armamentarium.

References

1. Ward, George Gray: *AM. J. OBST. & GYN.* 40: 158, 1940.
2. Flynn, C. W.: *Texas State J. Med.* 24: 279, 1928.
3. Schriener, B. F.: *Radiology* 17: 265, 1931.

of the myoma in three groups, excluding the Negro group. The first is the observation group, producing no demonstrable symptoms. They are simply kept under observation, almost regardless of size, although by the time they reach a size of a four months' pregnancy they do produce symptoms. The second is the younger women in the myomectomy group, in whom the childbearing factor is essential. The third group is the hysterectomy group comprising practically all the rest.

Now we have had marked necrosis and one case of gangrene in a fibromyoma of about the size of a four months' pregnancy, following about 2,000 mc. hr. of irradiation. One was a disastrous case with the loss of the patient.

I have not had experience with the minor dosage suggested, giving 350 to 400 millicurie hours. I do not exactly see the rationality of this.

DR. HERBERT E. SCHMITZ, CHICAGO, ILL.—In an analysis of some 760 cases reported from our clinic we too decided that 1,800 mc. hr. was the ideal dose to cause a permanent cessation of the menses in a woman of menopausal age. If roentgen therapy or external irradiation is used, it takes 500 roentgens of x-ray in the midpelvis to cause the same effect and when you refer your patient to the radiologist be sure to specify the dose, otherwise she may be under- or overirradiated.

I feel that in infected cases it is very poor judgment to block the cervical canal. That brings up the question of pelvic inflammatory disease. You remember Dr. Polak's work on that subject and x-ray today is being employed routinely for inflammatory disease. We have a routine rule on our service that if a patient with radium in the uterine cavity has a temperature rise to 100.4° F. the radium is immediately removed. Then external irradiation can be continued in small dosage until you have given the desired dose without fear of spreading the infection.

The postoperative discharge following the use of radium lasts from six to eight weeks and has been so appropriately described as a "meat juice" discharge. It is very distressing to the patient and can be avoided if external irradiation is used in preference to radium.

There is a general tendency at the present time to substitute vaginal hysterectomy for radiation therapy in the treatment of benign bleedings. The argument used is that these hyperplastic cases of endometritis are potentially cases of carcinoma of the endometrium. This has not been my observation, and though surgery may have a mortality rate of only 0.5 per cent, we have no mortality rate with irradiation. The period of hospitalization is much shorter when irradiation is used and the end result is just as satisfactory.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—I have just noticed that I left out the most important group, and that is the abbreviation group, with tumors not larger than three and one-half months' pregnancy, at least not past 35, in submucous tumors associated with inflammatory disease and showing tendency to degeneration. That is probably the largest group we have.

DR. RONGY (closing).—Many of the questions raised in the discussion are fully covered in the paper, which time did not permit me to read in its entirety.

I do not wish to convey the impression that I am especially interested in the treatment of uterine bleeding with radium. I am more interested in gynecologic surgery, but these cases were selected from a large number of patients, who consulted me for uterine bleeding. I resorted to radium therapy only in patients who had contraindications for a major surgical operation or when the fibroid was so small that there could be no doubt of a favorable result.

I, too, was fearful of performing a plastic operation on the vaginal vault in conjunction with radiation. After I did one case and encountered no trouble, I followed this in all cases where such procedures were indicated. Sixty-five of these

necrosis, infection, and obstruction and pyometra occasionally encountered in intra-uterine therapy may more than offset the advantages of intrauterine radium over deep roentgen therapy.

DR. WILLIAM H. VOGT, St. Louis, Mo.—Occasionally I use radium for uterine bleeding and the remarks to follow are not intended to condemn the procedure. My discussion is directed chiefly toward the contraindications for its use.

We all recognize that one of the contraindications is submucous fibroids of the uterus. I do not know of any way whereby one can be certain that such a condition exists or is absent, particularly if these tumors happen to be small.

Another contraindication, which is always stressed, is pelvic inflammatory disease. If we use radium in the presence of pelvic inflammation we are likely to set up an acute process, and perhaps even a severe peritonitis. We have all operated upon patients for fibroids and then, to our surprise, encountered pelvic inflammatory disease, which we had not suspected before the operation. Because my sense of touch in gynecologic practice does not seem to be developed to that degree that I can always say that there is or is not an inflammatory disease of the adnexa present, I hesitate to use radium more frequently in the treatment of so-called benign uterine bleeding or in small fibroids. When I do use it I still do so with some fear and trepidation.

DR. JAMES E. KING, BUFFALO, N. Y.—I believe that the question of irradiation in benign disease of the uterus, or simple bleeding, should be divided into three sections: first, the hyperplasias; second, the fibroids which may be so treated; and, finally, the endometrial atrophy that gives rise to very slight bleeding and which creates a suspicion of malignancy.

So far as hyperplasia is concerned, we frequently see these cases in young women, with the exception of a few, and I think it is very wrong to do anything to castrate them. Therefore, I have always given small doses, perhaps not more than 400 millieurie hours, and usually 350. It is surprising how that will frequently afford several years of comparatively normal menstruation.

So far as fibroids are concerned, I never treat one larger than a three months' pregnancy with radium. And there again, in the bleeding occurring during the childbearing life of the woman, we are handicapped by fear of giving a large dose which might cause castration. According to my figures on the cases I reported a number of years ago there were approximately 25 per cent of my own patients that came back to me requiring a hysterectomy. How many in my series there were that were done by others I do not know, but that is not a very large percentage and I think it bears out the fact that radium is helpful in many of these fibroid uteri.

Another thing that I find divergent from Dr. Rongy's finding was the occurrence of hyperplasia in connection with these fibroids. In my series it occurred in about 70 per cent of all these fibroids. Of course, the uterus was always curetted and the pathologist is responsible for the report of about 70 to 75 per cent having hyperplasia. Therefore, when we say that the bleeding is caused by the fibroid I think that is, in the main, wrong. I think it is because these cases have a hyperplasia associated with the fibroid, and we treat the hyperplasia with the fibroid the same as we would were the fibroid not present.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—In our work we have to divide our fibroid cases into two racial groups, the Negroes and the whites. In the first we have a type of fibromyoma which appears early in life, is almost always multiple, with a great tendency to multiplication of the nodules and with a tremendous growth. In the white women we have about the same conditions that you have in the North. In the Negroes we find an almost universal association of inflammatory disease which we have to take into account when considering irradiation. We think

THE GLYCOGEN INDEX IN THE MENOPAUSE*

A Study of Certain Estrogen Functions Based on a New Method of Staining Vaginal Smears

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WITH the large number of natural and synthetic estrogen products now available commercially, there is pressing need for objective evidence of their comparative value. Attempts to fulfill this need through laboratory experiments upon spayed animals and clinical studies based upon the relief of menopausal symptoms have, for the most part, yielded evidence of only relative value. Variations in species susceptibility¹⁻³ to estrogens have produced a confusing array of biologic standards. Similarly, the variable and often purely psychogenic factors⁴ which characterize climacteric complaints have led to interpretations which Frank⁵ once described as dependent "about equally on the impressions of the physician and of the patient." Since materials for clinical use must logically be based upon human requirements and responses, the need for objective human yardsticks to take the place of clinically useless biologic standards and questionable appraisals based on symptomatic relief, is evident.

The introduction of the vaginal smear method for studying estrogenic response by Papanicolaou^{6, 7} is an important contribution which, partially at least, provides the means for an objective clinical approach to this problem. A new adaptation of Papanicolaou's procedure was recently presented in a preliminary report⁸ of the iodine vapor method of staining vaginal smears for glycogen. Further personal experience⁹ and an independent study by Willson and Goforth¹⁰ have substantiated the usefulness of this simple test for appraising estrogen responses. A more detailed description of this new technique, an account of its application in an investigation of vaginal glycogen in the menopause, and a study of estrogen responses to various commercial preparations are presented in this report.

The Iodine Vapor Method

The basis of this test, namely the presence of glycogen in the normal vaginal epithelium and its dependence upon estrogenic activity, is well

*Presented, by invitation, at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10 to 12, 1942.

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patients had plastic operations. The healing was not interfered with, nor was the convalescence delayed, and the results on the whole were good. I believe it is an ideal method to follow in patients who suffer from uterine bleeding and require vaginal repair.

I truly believe that we have failed to take into consideration the psychologic attitude of both husband and wife in the treatment of these patients. I know of many marital tragedies resulting from the removal of the uterus and ovaries. Often the husband's attitude to his castrated wife undergoes a change when he is informed that one or more of the genital organs have been removed. Their sex life is definitely influenced by it, and it is therefore necessary in certain types of patients to conserve the organs and not remove them.

With the exception of one case, I never encountered intrauterine necrosis, infection or pyometra as a result of intrauterine radiation. If the indications are properly set the chances are these complications are not likely to occur.

Somehow, I still cannot agree with Dr. Campbell that large fibroids should be treated by intrauterine radiation. However, he is correct in stating that "generally speaking it is not the size of the tumor that counts, but whether or not it presents signs of degeneration."

The question raised by Dr. Vogt in connection with submucous fibroids is pertinent. I do, however, believe that submucous fibroids can be easily detected by the curette and that radium should never be used when submucous fibroids are suspected.

Our experience with hyperplasia of the endometrium in connection with uterine fibroids differs materially from that of Dr. King, who found this condition in 70 per cent of all his patients. This is also true of his statement that 25 per cent of his patients later required hysterectomy. Of the 350 cases we had only five failures, upon whom hysterectomy had to be performed.

I fully agree with Dr. Cooke that once infection either in the parametrium or in the genital organs is suspected, no form of radiation should be utilized.

I was glad to hear Dr. Schmitz state that he considered 1,800 mc. hr. the proper dose in this group of cases. I agree with him in his condemnation of vaginal hysterectomy as a treatment for benign uterine bleeding, instead of radiation therapy, especially when many of these patients require repair of the vaginal vault.

are located in the central portion of the cells. Varying numbers of smaller and more rounded epithelial cells taking a deep brown color are also found with some degree of regularity. In contrast to the idiophilic brown cells, a large number of nonglyeogenic, unstained or lightly stained lemon-yellow cells of irregular size and shape and with poorly defined borders, make up the balance of the picture. Variations in the proportion of iodophilic and non-iodophilic cells have been observed during various phases of the normal cycle, although an exact relationship has not as yet been determined. The greatest number of deeply stained iodophilic cells has been observed during the follicular phase.

2. *Glycogen Deficiency (Glycopenia)*.—Smears from women during various stages of the menopause as well as from children prior to puberty are distinguishable macroscopically by the absence of the rich brown color of the stained smear. Such slides have a lemon-yellow, buff, brownish-yellow, or light brown appearance, depending upon the degree of glycogen poverty. In extreme grades of vaginal atrophy, as in very young children, or in advanced stages of the menopause, smears consist almost entirely of amorphous cellular debris and varying numbers of yellow squamous cells; small round cells ("deep cells") are also present. In less advanced stages of ovarian hypofunction (as in earlier phases of the menopause and in prepubescent children) glycogen deficiency is discernible by the presence of mottled cells, i.e., cells containing small, irregularly distributed brown deposits at the cell margins and in the cytoplasm. The brown color rarely involves the entire cell as in sexual maturity. The few cells which stain diffusely are smaller than normal and stain less intensely than in high estrogen states. Unstained, irregularly shaped cells, typical of the superficial layer, are also present in abundance. In early stages of the menopause, smears indistinguishable from the normal are observed frequently.

Grading of Smears

The following system of grading, based on glycogen content and intracellular distribution, is proposed for classifying smears stained by the iodine vapor technique. A somewhat similar scheme, based on the proportions of iodophilic and noniodophilic cells, was employed by Willson and Goforth.*

Grade I.—Complete glycopenia. Smears of this type contain only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris. In extreme degrees there is marked paucity of epithelial elements (Fig. 1).

Grade II.—This grade is marked by a greater abundance of epithelial elements than Grade I. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm ("mottled cells"). Diffusely stained brown cells, usually of the small round variety ("deep cells") may also be present in small numbers. Many glycopenic yellow cells are also present (Fig. 2).

Grade III.—A further increase in cell numbers is evident in this grade as compared to the preceding. The cells are larger and more regular. The diffusely stained cytoplasm has a light brown color. Noniodophilic yellow cells are also present in abundance (Fig. 3).

* +, only an occasional glycogen-containing cell.
 ++, less than one-third of the cells contain glycogen.
 +++, from one-third to two-thirds of the cells contain glycogen.
 +++, more than two-thirds of the cells contain glycogen.

established.* The staining technique, moreover, is based upon a specific color reaction resulting from the well-known affinity between iodine and glycogen.† The simplicity of the staining technique, compared to the time-consuming and technically difficult procedures of Papanicolaou and Schorr, and its lack of dependence upon microscopic skill in identifying the bizarre and varied cytologic forms in vaginal smears, render this method suitable both for clinical investigation and office practice.

Technique

1. *Preparation of Smears.*—A cotton applicator is inserted into the vagina and twirled lightly (one complete rotation) against the vaginal wall. The cotton end of the applicator is then rolled lengthwise over the surface of a clean glass slide. By rolling, rather than rubbing, a uniformly thin film of cells, with minimal clumping and cell distortion, results. The film dries almost immediately and may be stained at once.

2. *Staining of Smears.*—Staining is accomplished simply by laying the slide, face down, over a shallow dish containing Lugol's solution. Iodine vapors which arise insensibly from the solution suffice to stain the glycogen-containing cells in two or three minutes. Microscopic examination may be carried out immediately. Although stains made in this manner fade in twenty-four to forty-eight hours, re-staining by the same method may be carried out repeatedly if subsequent examinations are desired. (A recent survey of smears made more than one year ago showed the same intensity of staining observed in original examinations.)

Microscopic Appearance

1. *Normal Glycogen Content.*—Vaginal smears from women with normal glycogen content are recognizable even macroscopically by the deep brown color of the stained slide. The microscopic picture shows a preponderance of large, flat, polygonal cells with rich brown cytoplasm. The unstained nuclei, recognizable as small, round, translucent bodies,

*The high glycogen content of the normal vagina during sexual maturity, its absence or diminution in menopausal and juvenile atrophy, and its close relationship to vaginal acidity have long been recognized. The dependence of normal glycogen values upon ovarian function and the ability of estrogen therapy to restore these values in the atrophic and glycopenic vaginal mucosa, have been conclusively demonstrated as a result of many investigations, notably those of Lewis,^{11, 12} Cruikshank and Sherman,¹³ Davis,^{14, 15} Adair and Hesseltine,¹⁶ Cotte, Mileff and Meyer,¹⁷ and McLaren.¹⁸ These studies were based upon histologic examinations of tissues obtained post mortem and by biopsy and stained for glycogen by the usual histochemical methods. Herrnberger and Horstmann¹⁹ by staining vaginal smears of children with Best's carmalum method, were able to demonstrate an increase in intracellular glycogen following the oral administration of estradiol benzoate. A good summary of the literature pertaining to vaginal glycogen is contained in their publication.

†The well-known affinity between iodine and glycogen has long been employed in histologic methods (Langhans, 1890). Merkel²⁰ recommended dilute Lugol's solution as a means of detecting vaginal epithelial cells in medicolegal investigations. He described the chocolate-brown or terra cotta color of the glycogen-rich vaginal cells which differentiates them from epithelial elements from other parts of the body. Schroeder, Hinrichs and Kessler²¹ confirmed Merkel's description in their studies of vaginal glycogen as related to bacterial flora and vaginal acidity. Both Merkel and Schroeder noted variations in glycogen content as well as occasional complete absence. In instances of "vaginosis." Mathes,²² according to Schroeder, utilized iodine in crude colorimetric determinations of vaginal glycogen by irrigating the vagina with Pregel's solution. Schroeder, Hinrichs and Kessler attempted more accurate colorimetric studies by comparing the color reactions obtained (from the addition of one drop of Lugol's solution to a given quantity of diluted vaginal secretion) with a color chart representing reactions to specific amounts of pure glycogen in solution. Krumm²³ and Palmer²⁴ advocated the use of Schiller's iodine test for carcinoma (which depends upon the absence of glycogen in areas suspected of malignancy) as a means of determining the "absence of the follicular secretion."

The iodine vapor method was a chance discovery while investigating the possibilities of Merkel's technique in determinations of estrogen states from vaginal smears.



Fig. 4.

Fig. 3.



Fig. 2.

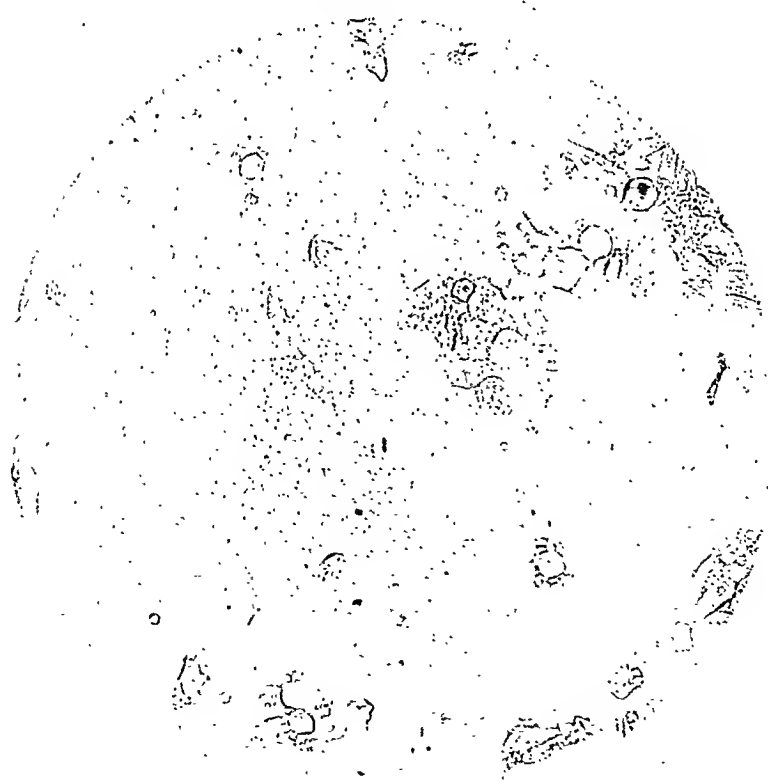


Fig. 1.

TABLE II. AGE DISTRIBUTION OF GLYCOGEN GRADES IN ARTIFICIAL MENOPAUSE AND NATURAL MENOPAUSE OF KNOWN DURATION

AGE	NATURAL MENOPAUSE (21)				ARTIFICIAL MENOPAUSE (22)			
	GRADE I	GRADE II	GRADE III	GRADE IV	GRADE I	GRADE II	GRADE III	GRADE IV
75	2							
70	1	1						
65	2				1			
60	1	2	2					
55	1	2	1				1	
50			2			4		
45	1	1				3	1	
40			2		2	6	1	
35						1		
30					1	1		
Total	8	6	7		4	15	3	
Per cent	38.0	28.7	33.3		18.1	68.1	13.6	

TABLE III. DISTRIBUTION OF GRADES ACCORDING TO DURATION OF MENOPAUSE

YEARS OF MENOPAUSE	NATURAL MENOPAUSE				ARTIFICIAL MENOPAUSE			
	I	II	III	IV	I	II	III	IV
35-40	2							
30-35	2							
25-30	1							
20-25	1	1						
15-20	1	1	1			1		
10-15		2			1	3		
5-10	1	2	3		1	3	1	
1-5			3		2	8	2	
Total	8	6	7		4	15	3	
Per cent	38	29.7	33.3		18.2	68.2	13.6	

Table I shows the distribution of the four glycogen grades *according to age* in 108 women with natural menopause. Table II compared the grade distributions (according to age) in the 22 women with artificial menopause to the 21 subjects with natural menopause of known duration. Table III compares the distribution of the four grades *according to years of duration* in natural and artificial menopause.

Discussion

Analysis of the data presented in Tables I to III shows that glycogen in variable amounts is found in all age groups of menopausal women regardless of whether the climacteric was spontaneous or induced. Complete absence of all traces (Grade I) was noted in 21.5 per cent of the *entire series of 130 patients, including both natural and artificially induced menopause* (108 patients in Table I plus 22 with artificial menopause in Table II). Advanced glycopenia, but with minimal traces of glycogen (Grade II) was present in 48.4 per cent of the combined series; moderate deficiency, or, from the other point of view, moderate estrogen stimulation, as shown in Grade III, was present in 27.6 per cent. Evidence of apparent estrogen *sufficiency*, as indicated by Grade IV smears, was present in 3 patients (2.3 per cent), aged 57, 63, and 71 years, re-

Grade IV.—This grade is easily recognized by the presence, almost exclusively, of large, flat, deeply stained brown iodophilic cells, present singly or in large clumps. This grade represents maximal estrogenic effect and corresponds to the smear of the normal proliferative or follicular phase (Fig. 4).

The Vaginal Glycogen Index of Estrogenic Activity in the Menopause

Studies of the menopausal state within recent years have repeatedly indicated that cessation of the menses is not accompanied abruptly by a disappearance of estrogens. Continued elaboration by the ovaries or other endocrine organs, such as the adrenals, or the action of estrus-inducing agents derived from extrinsic sources (food), have been suggested as reasons for postmenopausal persistence of estrogens in the blood and urine,²⁵⁻²⁷ postclimacteric endometrial hyperplasia,²⁸ normal vaginal smear pictures,^{18, 29} and varying amounts of vaginal glycogen^{18, 19} after the natural and artificial menopause. According to Salmon and Frank,²⁹ only 40 per cent of postmenopausal smears gave negative evidence of estrogenic function. McLaren's study¹⁸ showed normal smears in 78 per cent and led to the conclusion, also reached by Bennett and TeLinde,³⁰ that vaginal smears have no value as guides to estrogenic therapy as claimed by Papanicolaou and Schorr.⁷

To determine whether smears stained for glycogen by the iodine vapor method gave similar evidence of residual estrogenic activity, studies were made of 130 postmenopausal women with chronic, nonfebrile diseases and ranging in age from 33 to 97 years. With the exception of 22 (16.9 per cent) whose menopause had been induced by irradiation or surgical castration, the remaining 108 entered the climacteric spontaneously. Of the latter, 21 were able to give reliable information as to the last date of menstruation. Vaginal smears, after iodine vapor staining, were graded according to the system described above. The results are summarized in Tables I to III.

TABLE I. DISTRIBUTION OF GLYCOGEN GRADES IN NATURAL MENOPAUSE ACCORDING TO AGE IN 108 WOMEN

AGE	GRADE I	GRADE II	GRADE III	GRADE IV
100				
95		1		
90	2	1		
85	3	2	2	
80	1	6	2	
75	4	3	4	1
70	3	12	1	
65	4	5	5	1
60	2	5	3	
55	1	6	3	1
50	2	5	6	
45	2	1	4	
40		1	3	
Total	24	48	33	3
Per cent	22.2	44.4	30.6	2.8

While the *absence* of glycogen in the vaginal epithelium is generally accepted as evidence of estrogenic deficiency, the possible effects of concomitant disease, constitutional defect, or local disorders preventing the mobilization of glycogen by estrogens must also be recognized. The findings of earlier writers³²⁻³⁴ that glycogen poverty is frequently associated with tuberculosis, chlorosis, hyperthyroidism, asthenic habitus, and infantilism is augmented clinically by the well-known association of menstrual disorders³⁵ and vaginitis³⁶ in women with debilitating conditions. Sharp and Mack³⁷ have similarly shown a frequent association of hemopoietic phenomena and endocrine disorders in women. The general assumption in most clinical discussions of these relationships is that ovarian function (i.e., estrogen elaboration) is suppressed by the concomitant disease. The fact, however, that purely local infections of the vagina (such as *Trichomonas vaginalis* vaginitis) are often associated with glycogen poverty in the presence of normal menstrual function, suggests the presence of local or general "antihormonal" factors, rather than primary ovarian failure, as causes of estrogen deficiency and glycopenia in certain instances.

This explanation was strongly suggested by our observation that vaginal glycopenia in sexually mature tuberculous women was present only during the febrile and rapidly deteriorating phases of the disease. When the disease was arrested or stationary, normal glycogen values were consistently present. Women with normal glycogen smears at the onset of the disease frequently became completely glycopenic in the terminal, highly febrile stages. Our investigations⁹ with estrone administrations to menopausal tuberculous women, furthermore, showed progressive diminution of vaginal glycogen response as the patient's clinical status deteriorated. This decline was invariably accompanied by fever. One patient (a surgical castrate), with rapidly progressive generalized tuberculosis, remained completely refractory to large doses of estrone administered orally as well as parenterally over a period of five weeks. Daily vaginal smears and post-mortem histologic examination of the vaginal mucosa revealed complete lack of glycogen. Another patient, studied at intervals over a period of nine months, was remarkably "estrogen sensitive" until the last month when, during the terminal febrile phase of her disease, she showed progressive loss of response to identical doses. Herrnberger and Horstmann similarly noted abrupt cessation of glycogen response to the administration of estradiol benzoate with the development of intercurrent pneumonia in a previously estrogen sensitive child. Our observations and those of Herrnberger and Horstmann¹⁹ indicate that some toxic factor, such as fever, may prevent the metabolic activity of estrogen or actually cause its destruction. This interpretation, rather than that of ovarian inhibition, would seem to offer an explanation of the occurrence of amenorrhea and vaginal glycopenia in some wasting diseases.

spectively, who had entered the menopause spontaneously. Glycopenia, indicative of advanced or complete estrogen deficiency (Grades I and II) was thus present in approximately 70 per cent, whereas evidence of moderate and approximately normal vaginal stimulation (Grades III and IV) was present in 30 per cent. The discrepancy between these findings and those indicated by Salmon and Frank and by McLaren, seems to indicate that the glycogen index may be a more sensitive indicator of estrogenic activity than cell morphology. Willson and Goforth's study also showed that glycogen increase preceded change in cell types in their investigations of the effects of stilbestrol on the vaginal mucosa, as determined by the iodine vapor technique.

Table II shows a similar proportion in the group of women with natural menopause of known duration: Moderate stimulation, 33.3 per cent; estrogen deficiency, 66.6 per cent. The group with artificially induced climacteric, on the other hand, showed moderate estrogen stimulation in only 13.6 per cent and advanced and complete glycopenia in 86.2 per cent. While the series is too small to admit sweeping conclusions, there is apparent evidence to indicate that postmenopausal estrogen stimulation, which normally persists for some time after the natural menopause, is reduced by castration. This would seem to show that the ovary is the chief source of estrogen elaboration after the menopause. Possible extraovarian sources of estrogen are indicated by the persistence of moderate stimulation in 13.6 per cent.

The probable primary importance of the ovary as the source of postmenopausal estrogen stimulation is shown (Table III) also by the fact that Grade III reactions were observed as late as twenty years after the natural menopause, whereas the same degree of estrogen stimulation was present no longer than ten years after castration.

Further studies with larger series of castrates and women with natural menopause of known duration are necessary to provide precise data. The simplicity of the iodine vapor technique makes it suitable for such studies in institutions where appropriate material is available.

Glycopenia in Vaginitis and Febrile Conditions

While Adair and Hesseltine¹⁶ noted increases in vaginal glycogen following the local administration of lactose in senile vaginitis and vaginal trichomoniasis, the recent study of Willson and Goforth indicates that excess of ingested carbohydrate does not influence the glycogen content of women with postmenopausal glycopenia vaginal atrophy. The promptness, however, with which Willson and Goforth were able to induce glycogen increases by the administration of estrogen, regardless of carbohydrate intake and often before changes in cell morphology could be recognized by the Schorr technique,³¹ is further evidence that the glycogen index is a sensitive indicator of estrogenic activity.

this level for eight days. Return to pre-treatment grades occurred at approximately the same time (twenty-one days).

(b) *Estrone by Oral and Vaginal Routes* (Fig. 5, B, C, D).—Two subjects (M. P., aged 44 years; M. T., aged 66 years) received a total of 9.0 and 15.0 mg. of crystalline estrone, respectively, in 6 and 10 daily oral doses of 1.5 mg. each. Vaginal glycogen responses were closely similar. Maximal effects (Grade IV) were obtained in each instance on the seventh day. This effect was maintained eight days following the smaller (9.0 mg.) and fifteen days after the larger (15.0 mg.) amount.

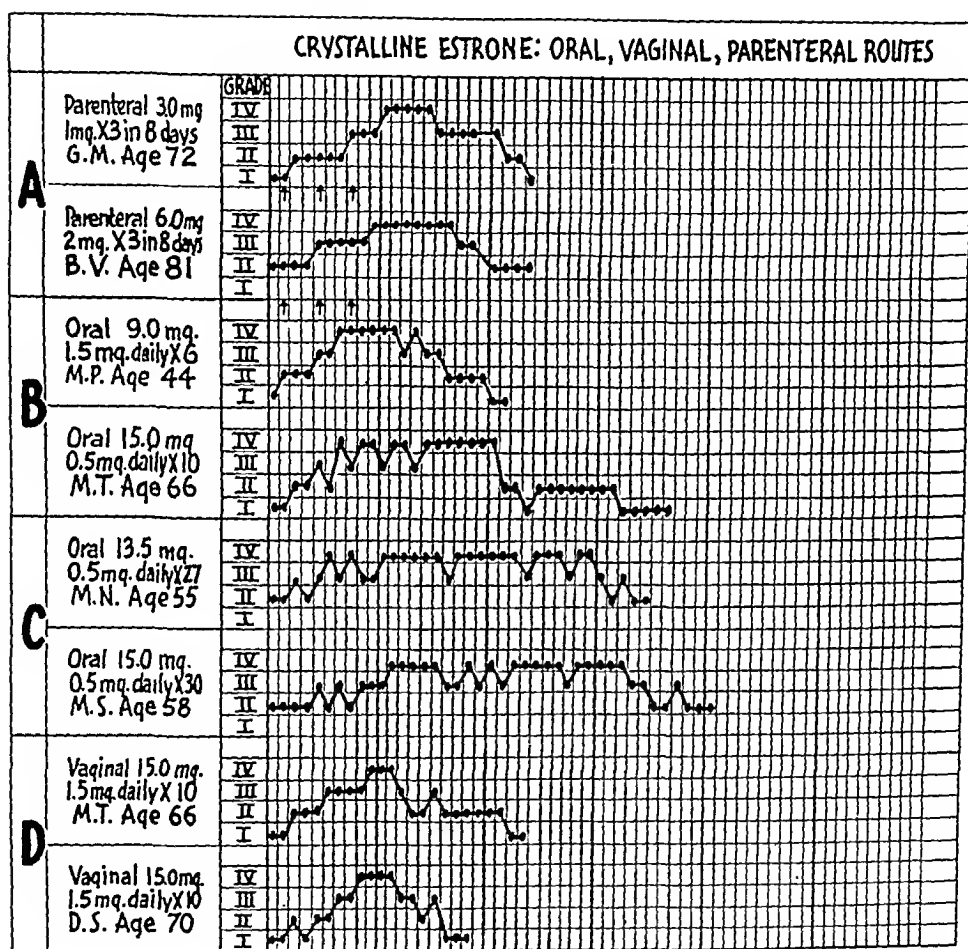


FIG. 5.

Two subjects (M. S., aged fifty-eight years; M. N., aged 55 years) were given 0.5 mg. of crystalline estrone orally for twenty-seven and thirty days, respectively. The corresponding curves again showed striking similarity. Sustained maximal effects (Grade IV) were obtained in each instance on the eleventh day and were maintained throughout the course of treatment with only minor fluctuations. Return to the pre-treatment grades became evident four days after cessation of treatment.

Two subjects (M. T., aged 66 years; D. S., aged 70 years) were each given 15.0 mg. of crystalline estrone in 10 equal daily doses (1.5 mg.

From the evidence cited above, it would appear that successful replacement therapy with estrogens should not be expected in febrile states. Moreover, it seems possible that many instances of nonspecific vaginitis may have their origins in glycogen poverty and consequent lowered resistance to ordinary bacterial invaders as a result not only of primary ovarian deficiency, but also of febrile states or local agents which counteract estrogenic functions. Finally, the importance of eliminating subjects with febrile conditions and vaginitis, when utilizing the vaginal glycogen index in assay studies, must be emphasized.

The Vaginal Glycogen Index as a Basis for Human Assay

The lack of vaginal atrophy as well as glycopenia in the early, symptom-producing phases of the menopause in most women, indicates the limited clinical value of vaginal smear methods as guides to symptomatic treatment. The sensitivity of the vagina to small amounts of estrogen, however, and the ease with which the vaginal glycogen response can be visualized by the iodine vapor technique, suggest the usefulness of this method of approach in controlling therapy of senile and juvenile vaginitis as well as in determinations of the relative potencies of various commercial estrogens as judged by their effect upon menopausal women with advanced glycopenic vaginal atrophy. Applications of this procedure in studies of oral, parenteral and vaginal administrations of estrone, as well as of stilbestrol, have already been reported.^{9, 10}

The present study includes: (a) Determinations of estrone responses with amounts commonly employed in parenteral therapy; (b) comparisons of reactions to identical amounts of estrone administered by the oral and vaginal routes; (c) comparisons of glycogen responses to identical amounts of estrone, estriol, alpha-estradiol, diethyl-stilbestrol, sodium estrone sulphate, and estrone-estriol mixture when given by the oral route.*

(a) *Estrone by Injection* (Fig. 5, A).—Two postmenopausal subjects (G. M., aged 72 years; B. V., aged 81 years) received 3.0 and 6.0 mg. of crystalline estrone, respectively, given in three equal injections at four-day intervals. The smaller amount was administered in three injections of 1.0 mg. crystalline estrone dissolved in oil (10,000 i.e.); the larger amount was given in three injections of 2.0 mg. of crystalline estrone in aqueous suspension. The resulting vaginal glycogen responses (as determined from daily vaginal smears), when plotted graphically, give practically identical curves. The smaller dose (3.0 mg.) produced a maximal reaction (Grade IV) on the eleventh day after the onset of treatment and maintained this effect for five days. The larger amount (6.0 mg.) produced its maximal response on the tenth day and sustained

*The estrogen preparations employed in this study were supplied as follows:
Estrone, estriol, estrone-estriol mixture by Parke, Davis and Co., Detroit, Michigan.
Alpha-Estradiol by Roche Organon Inc., Nutley, N. J.
Diethylstilbestrol and Sodium-estrone sulfate by Ayerst, McKenna and Harrison, Rouses Pointe, N. Y.

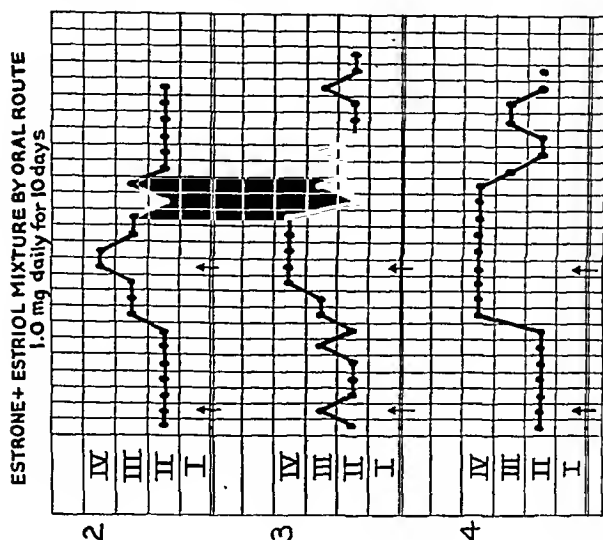


Fig. 8.

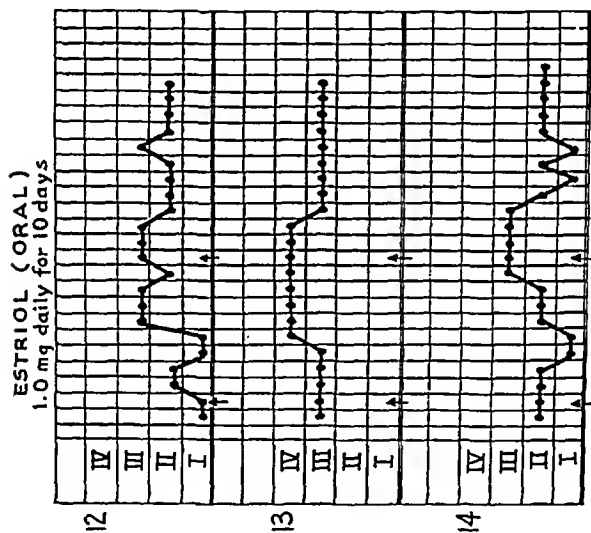


Fig. 7.

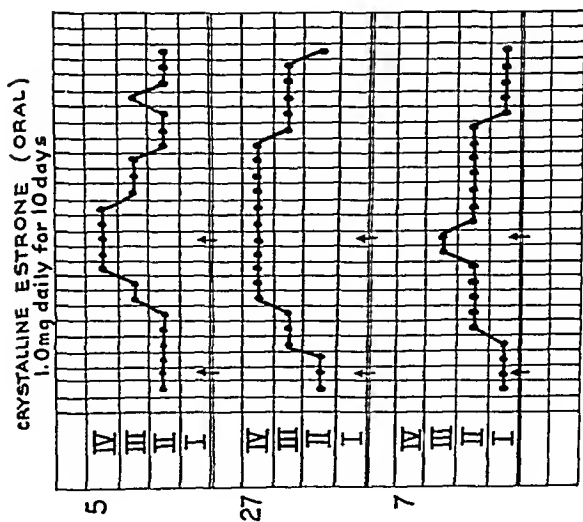


Fig. 6.

each) for ten days by the vaginal route. A striking similarity of the resulting curves is evident. Maximal effects appeared on the ninth and tenth days and were maintained for three and four days, respectively. Return to the pre-treatment states occurred on the nineteenth and twenty-third days. One of these subjects (M. T.) had previously received the same dosage by mouth. Comparison of the vaginal glycogen curve, following oral administration (see above), and the curve after vaginal administration, shows a similar though more sustained reaction from oral administration of the same amount.

(c) *Estrone, Estriol, Estradiol, Stilbestrol, Sodium Estrone Sulfate, and Estrone-Estriol Mixture by Oral Administration* (Figs. 9 and 11).—Eighteen subjects (three for each of the above-named preparations) received totals of 10 mg. of estrone, estriol, estradiol, stilbestrol, and estrone-estriol mixture, respectively, in 1.0 mg. doses for a period of ten days; the sodium estrone sulfate preparation (supplied in 1.25 mg. tablets) was given daily for eight days (total 10.0 mg.). Three additional women of the same age range (age 66, 72, 81) each received 1 gr. of desiccated thyroid (U.S.P.) daily for ten days to serve as controls. No change in the vaginal glycogen content was observed from daily vaginal smears in the control group, whereas all who received the oral estrogen products showed readily demonstrable, though quantitatively variable, responses. No toxic side-effects were noted in any of the 18 women receiving estrogen therapy.

Estrone.—One milligram doses of crystalline estrone dissolved in corn oil produced typical responses noted in the previous studies. Maximal (Grade IV) reactions were observed in two patients (Cases 5 and 27) on the eighth and sixth days of treatment, respectively; Patient 7, a less sensitive subject, attained only a Grade III reaction on the ninth day (Fig. 6).

Estriol.—One milligram doses of estriol uniformly showed a less pronounced estrogenic action than identical amounts of estrone by mouth. The maximal reactions obtained were Grade III, indicative of only moderate estrogenic effect (Cases 12 and 14); this grade was attained in six to nine days and was maintained, respectively, for five and six days. Patient 13, who had a Grade III reaction at the onset of therapy, reached a Grade IV effect in five days and maintained this stimulation for eight days (Fig. 7).

Estrone-Estriol Mixture.—A preparation containing 0.5 mg. each of estrone and estriol was given daily for ten days. Grade IV responses were obtained in all three subjects and were maintained steadily for two, five, and nine days, respectively. The resulting curve closely stimulates that for estrone, and indicates a greater potency than that of estriol in the same amount (1.0 mg.) (Fig. 8).

Alpha-Estradiol.—One milligram doses daily for ten days produced a maximal effect in all three subjects on the tenth, eleventh, and twelfth days, respectively. Grade IV reactions were sustained from two to six days. Except for variations in sustaining reaction, the effect compares closely to that obtained with identical amounts of estrone (Fig. 9).

Diethylstilbestrol.—One milligram doses daily for ten days produced maximal effects in all three subjects in four to nine days though maintenance at an even level (as with estrone and estradiol) was not obtained in any instance (Fig. 10).

Sodium Estrone Sulfate.—One and one-fourth milligram doses daily for eight days (total 10.0 mg.) produced a maximal (Grade IV) reaction

in two of three subjects on the ninth day; the third subject attained only a Grade III reaction on the ninth day. A sustained maximal effect of five days was obtained only in one instance (Case 22) (Fig. 11).

Discussion

The striking uniformity of the vaginal glycogen response to estrone by the parenteral, vaginal and oral routes of administration, also shown in previous studies^{8, 9} would seem to recommend this substance as the basis for comparisons of other estrogens in human potency determinations. However, until the minimum amount of estrone capable of producing and sustaining a maximal (Grade IV) reaction has been determined, comparisons must be limited to the effects obtained with identical weighed amounts, arbitrarily chosen.

Determinations by the glycogen index have thus far indicated that the minimal effective dose of estrone capable of producing and maintaining a maximal reaction ten days is probably less than 3.0 mg. when administered by injection and less than 5.0 mg. when given by the oral route. Further fractionation of dosage is necessary to determine these limits.

Our investigations have indicated further that oral administration generally seems to evoke a more prompt, parenteral administration, a more prolonged reaction. Moreover, we have shown also that daily divided dosage, exerted a more prolonged effect when given by mouth, than identical total amounts ingested at once.⁹ Besides the striking demonstration that estrone (contrary to general belief) is highly effective by the oral route, our glycogen determinations also show the apparent superiority of this route to vaginal administration.

Due to increasing interest in oral estrogen therapy and the evident need of a standardization procedure employing the human subject, we were encouraged to apply the iodine vapor technique in a comparative study of various other estrogen preparations. From these studies (Figs. 6 to 11), the weak estrogenic activity of estriol as compared to estrone given orally is immediately apparent. Alpha-estradiol, on the other hand, compares favorably with estrone, whereas stilbestrol, a synthetic estrogen, in equal amounts exerted a prompt though poorly sustained glycogen response. Ferin³⁸ has also noted this irregular response to stilbestrol in vaginal smear studies comparing this substance to natural estrogens. The apparent near equality of estrone and stilbestrol in estrogenic potency (when compared in equal oral dosage) is significant in the light of previous estimates by other methods, that oral stilbestrol is from 2.5 to 25 times more active than estrone by injection.^{39, 40} Sodium estrone sulfate, while giving evidence of strong estrogenic action, manifested marked variation in the glycogen responses in the trials thus far completed. Further tests of this substance are necessary to determine its comparative value. Estrone-estriol mixture (0.5 mg. of each in oil)

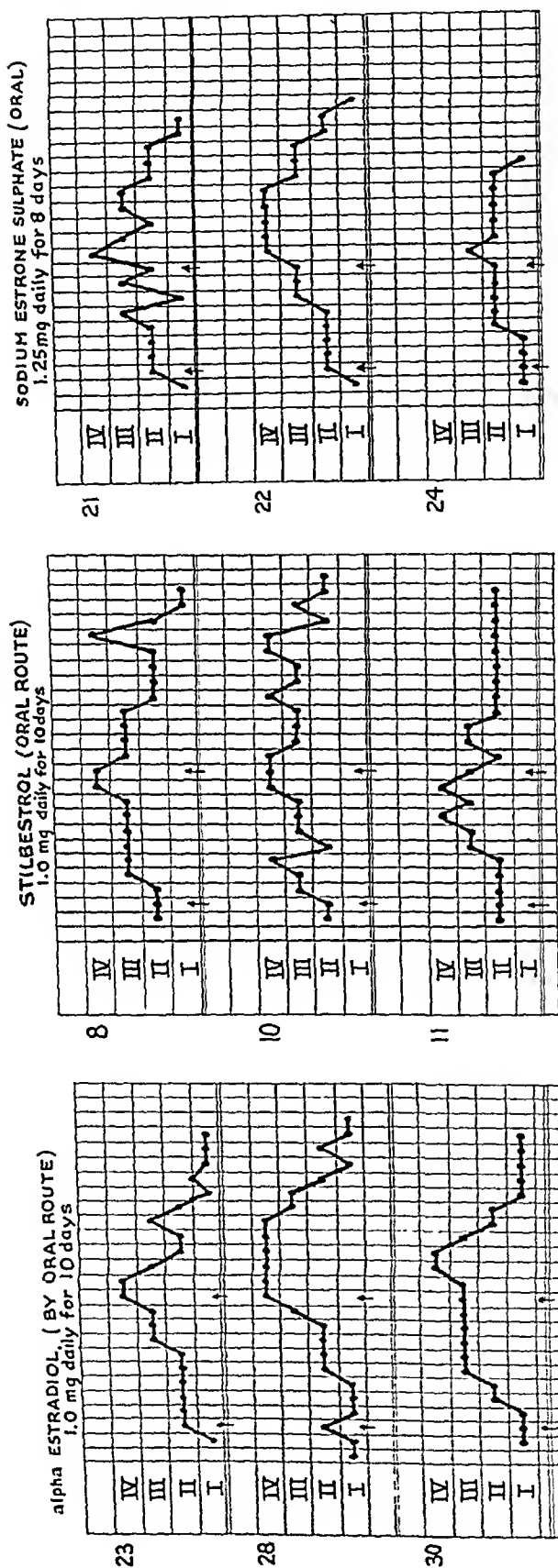


Fig. 9.

Fig. 10.

Fig. 11.

4. The clinical usefulness of vaginal smear methods (including the glycogen index) is at present limited largely to the control of estrogen therapy in vaginitis and to clinical investigations of estrogen potencies in suitable human subjects with advanced menopausal atrophy.

5. Experience with the glycogen index as a method for the comparative evaluation of estrogens in the human subject permits the following tentative deductions:

(a) Estriol, hitherto considered superior to estrone for oral medication on the basis of animal experiments, is less effective in the human than an equal weight of estrone.

(b) Alpha-estradiol, given as oral tablets, produces an estrogenic effect comparable to that induced by an equal weight of estrone in oil.

(c) Diethylstilbestrol in oil solution produces a more rapid glycogen effect when given by mouth than equal weights of estrone and alpha-estradiol. The glycogen response to stilbestrol fluctuates widely in comparison to the uniform effect obtained with estrone and alpha-estradiol.

(d) An estrone-estriol mixture (0.5 mg. of each in oil solution) orally, produces a glycogen reaction curve comparable to that induced by 0.5 mg. doses of estrone alone.

(e) Estrone produces uniform response and maintenance by all routes of administration, and can serve as a standard for comparative assays of estrogens in the human subject.

I wish to express my indebtedness to Dr. Henry Spitzer for valuable assistance in obtaining daily vaginal smears.

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produced an effect comparable to that obtained with 0.5 mg. of estrone alone, an observation which is contrary to the belief of Sevringhaus⁴¹ that "mixed estrogens known now as estrogenic substances, and estriol gluneronide appear to have an advantage per unit over the pure estrone, which is the chief constituent of the mixture."

Further fractionation of dosage is necessary to determine the minimum effective dose of each of these oral preparations. From the strikingly uniform responses obtained with oral estrone, it would appear that this substance can serve as the standard of oral estrogenic activity in the human test in the same manner as its characteristic reaction in animals has been made the basis of biologic assay methods.

Summary

The iodine vapor method of staining vaginal smears is presented as a rapid and simple means for determining the specific glycogen response to estrogen activity in the human subject. This method of clinical investigation is based upon observations that normal vaginal glycogen content parallels estrogen sufficiency, whereas diminution of glycogen (glycopenia) is indicative of estrogen deficiency.

To determine the incidence of glycogen poverty in postmenopausal women, vaginal smears from 130 climacteric women (after staining by the iodine vapor procedure) were graded according to glycogen content. The incidence of the four glycogen grades was calculated according to age, duration of the menopause, and the nature of the climacteric, whether spontaneous or artificially induced. The significance of the findings, in terms of other reports of postmenopausal estrogen elaboration, is discussed. The possible "anti-hormonal" effects of various systemic and local disorders (febrile states and vaginitis) upon estrogenic activity, are suggested by observations in tuberculous women.

Experience to date has established the usefulness of the glycogen index in estimating therapeutic response of estrogen therapy in juvenile gonorrheal and senile atrophic vaginitis. Evidence of its further value as a simple and sensitive indicator of estrogen activity in human subjects is presented in potency determinations of several commercial products.

Conclusions

1. The iodine vapor method of staining vaginal smears for glycogen provides a sensitive index of human estrogenic activity.
2. The persistence of variable amounts of vaginal glycogen in menopausal women provides additional evidence of continued estrogen elaboration by the ovary or from extragenital sources.
3. Although ovarian deficiency is the chief cause of vaginal glycopenia, possible "antihormonal" factors present in local and systemic disorders may be responsible for glycogen poverty, especially that observed in certain wasting diseases during sexual maturity.

oscillations noted during uterotubal insufflation which they believe to be manifestations of uterine muscle activity and not of the tubes.

In 1937 and 1938 two of my associates undertook to clarify this question by experimental work on the uterus and oviducts of live rabbits. The work of S. Wimpfheimer and M. Feresten^{4, 5} is of sufficient interest to be summarized briefly:

Procedure

Using 60 mature female rabbits weighing from 2 to 4 kilograms, they demonstrated that when a leak is made into the uterus, preventing the CO₂ gas from passing through the oviducts, the pressure oscillations become profoundly altered; that the isthmus and intramural portion of the oviducts influence the manometric fluctuations whether the insufflation proceeds through the uterus or through the tubes; no contractions take place when the oviducts have been cut away and the uterine segment alone is present and widely open. Furthermore, if the uterus is completely sidetracked by inserting the cannula directly into the uterotubal junction, the kymographic tracings continue practically unaltered.

The direct effect upon uterine and tubal motions was still further checked in the living rabbit by fastening fine hooks to segments of the uterine muscle and tubal muscle previous to insufflation and during insufflation. The action of the tubal and uterine muscle thus transmitted was recorded on a lampblack-coated paper on one kymograph while the dynamic changes taking place through insufflation were simultaneously recorded on another kymograph. This demonstrated that while the action of the tubal muscle was uninfluenced during insufflation there was a marked change in the action of the uterine muscle which exhibited shallow contractions in three instances and disappeared almost altogether in two instances. It should be pointed out that the tubes become partially distended by the CO₂ gas which has the possibility of escaping through the abdominal ends. The uterus, however, is more or less constantly under the same degree of distention contingent upon the resistance of the narrow apertures of the uterotubal junctions above and the mechanical obturation below. This last experiment would seem to be quite conclusive; nevertheless the question continues to be raised from time to time.

Among those who have questioned the above conclusions is Stabile,⁶ of Montevideo, who in a recent paper presents a painstaking inquiry into the nature of the oscillations observed during kymographic uterotubal insufflation. He feels apparently that the oscillations thus produced are due to changes in uterine and muscle tonicity which undergo certain variations due to regurgitation of the CO₂ gas from the tube as a sort of "garrulitas tubae." His conclusions are based upon observations he made upon living tubes and uterus at laparotomy. These observations have raised points which may well serve as the basis for discussion of the whole question of tubal vs. uterine contractions. Owing to the limited time and space allotted for this paper I shall not enter into all the moot questions.

Stabile believes that "because distention of the tube takes place coincident with the rise in pressure and the tubal soufflé heard by auscultation coincides with the drop in pressure, therefore tubal contractions

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955 FISCHER BUILDING

CLINICAL DIFFERENTIAL DEMONSTRATION OF UTERINE AND TUBAL CONTRACTIONS BY KYMOGRAPHIC UTEROTUBAL INSUFFLATION*

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FROM the beginning of uterotubal insufflation as a clinical non-operative test for tubal patency, it was noticed that during insufflation, pressure oscillations were manifest on the mercury manometer in most cases and absent in others. The oscillations were always present when the Fallopian tubes were found to be freely patent. In non-patent tubes, pressure oscillations were invariably absent.

Guthmann¹ was one of the first to observe and attempt to explain this difference in manometric fluctuations. However, it was some time before its full significance was realized. In 1925 adopting a kymograph to the insufflation apparatus, I began a more detailed study of this question, the results of which were published in November, 1927.²

In the work just referred to, it was demonstrated that the kymographic tracings observed during uterotubal insufflation are due to rhythmic contractions and relaxations of the tubal muscle; also that these pressure fluctuations are absent when the tubes are closed; and last, that the uterus is passive in the vast majority of cases during the insufflation, its contractility being inhibited by distention.

Two circumstances have led to renewed interest in this question. First, the statement by Knaus,³ and others, that the uterus undergoes changes in motility which vary with the interval of the ovulation-menstrual cycle; and, second, the recurring doubt by some as to the true nature of the

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uterotubal junction, the muscle sphincter of the intramural portion of the tube and its actual diameter.

In the course of its passage through uterus and Fallopian tubes the CO_2 gas meets with five resistances. The first has already been mentioned within the uterus; the second is the intramural portion; the third are the approximated walls of the tubes which are held in apposition by a certain tonicity of the tubal muscle; fourth, a sort of sphincter action at the isthmicoampullary junction and, fifth, a less developed sphincter at the fimbriated end.

Once the fimbriated end has been passed, the pressure drops. It must be borne in mind that the pressure mechanism of the apparatus insures a constant rate of flow of the insufflated gas. During the state of contraction, the tube becomes distended gradually and progressively from the uterine to the fimbriated end by the continuous insufflation of the CO_2 under a constant rate of flow until the fimbriated end is reached when the gas can escape into the peritoneal cavity. This we take to coincide with the moment of relaxation. Then contraction begins anew and the same mechanical process is repeated in a rhythmic fashion. If no contractions, followed by relaxations, took place, there should be no rhythmic oscillations of the manometer. That is to say if the CO_2 gas had only to overcome muscular tonicity it is conceivable that there would be an initial rise of pressure which should be enough to equalize and then exceed the dynamic resistance of the muscle. But once this was overcome there would be no other factor to prevent the continuous uninterrupted flow of gas through the tubes as the insufflating force is vastly greater than that encountered in the tube lumen. However, if one assumes that the tubes undergo rhythmic contractions, a fact borne out by visual observations on the intact organs and by numerous experiments on tubal muscle strips (Seckinger and Snyder,⁷ Corner,⁸ R. T. Frank⁹) then the oscillations observed on the kymograph during uterotubal insufflation in normal tubal patency are clearly accounted for.

Observations

The tubes contract as a whole and segmentally. If the tube of a rabbit is cut into segments from the fimbriated end toward the uterine end during uterotubal insufflation, it will be found that the isthmus and the intramural portion exhibit the most marked contractions while the force of the latter is relatively less in the ampullary portion and very weak in the fimbrial portion. If the sections are reversed in fimbrial (tubouterine) insufflation, practically the same results are obtainable. The same effects have been demonstrated in the surviving human Fallopian tubes.

In interpreting the graphs obtained by uterotubal insufflation, one must take cognizance of the fact that the CO_2 gas is introduced at a constant rate of flow and if the tubes had no inherent motility the CO_2 gas would be forced through them at a uniformly steady rate. There would be no pressure oscillations, the gas escaping at a constant flow rate of bubbles through the fimbriated ends and not intermittently as actually observed. When the tubal muscle undergoes contraction, the gas flow is momentarily intercepted by the tightening and narrowing of the tube lumen. This causes a rise of pressure. The moment the muscle relaxes the lumen is widened and the gas escapes with a drop

are ruled out relegating to the tubes a passive role." As this, in my opinion, is a basic contradiction it may be well to describe the action of the CO_2 gas and the reaction of the uterus and tubes to the CO_2 as it streams through the genital tract in the normal case. When CO_2 is insufflated into the uterus under airtight conditions at the cervix the uterus distends until such point where the narrow apertures of the uterine ostiae of the tubes are passed and at which point the gas must make its way through the tube lumen.

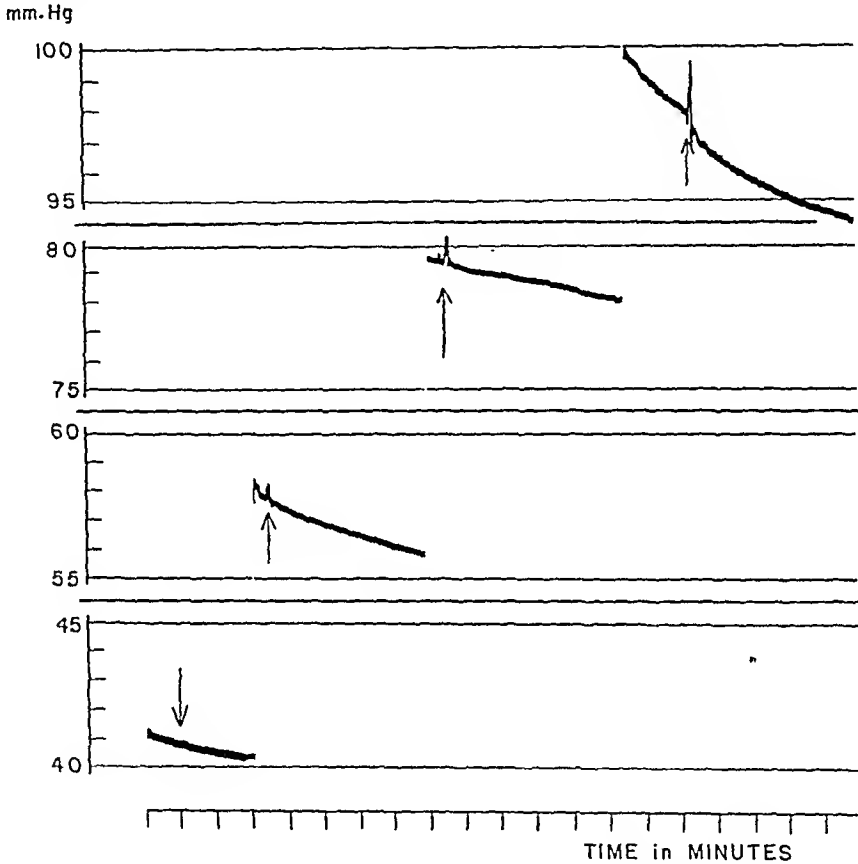


Fig. 1.—Showing degree of distention of the uterine cavity necessary for voluntary straining of the patient's abdominal muscles or manual compression of the abdominal wall to produce pressure effects on the uterus. In this case no pressure effects are visible at 41 mm. Hg while increasing effects are demonstrable at 58, 79, and 98 mm. Hg. The pressure necessary in this case to convert the virtual uterine cavity into a distended cavity is between 41 and 58 mm. Hg.

The pressure begins to rise the moment gas is forced into the uterus. As the uterine cavity is only virtual in the nonpregnant normal state, the uterine walls approximating each other and kept in apposition by the tonicity of the uterine muscle, a certain pressure is required to convert it into an actual cavity through distention. This varies according to my observations between 40 and 60 mm. Hg in the average case (Fig. 1). The pressure rises during the distention until such point when the uterine openings of the tubes are passed. The amount of pressure necessary to accomplish this depends upon the tonicity of the

tubes underneath the vesicouterine peritoneum. In this operation the fimbriated ends of the tubes are dislocated into the vesicouterine space where the edges of the tubes are sewn together at several points and fastened to the connective tissue as well as the uterine wall. If the tubes are insufflated a week or two after the operation the graph obtained will show complete absence of contractions although these were demonstrable before the tubes were transfixed. The CO_2 passes into the subperitoneal space where it produces the crepitus characteristic of gas collection. By means of uterosalpingography with any crystalloid iodine solution the transfixed dislocated Fallopian tubes may be visualized as well as the spill into the subperitoneal space of the vesicouterine fossa.

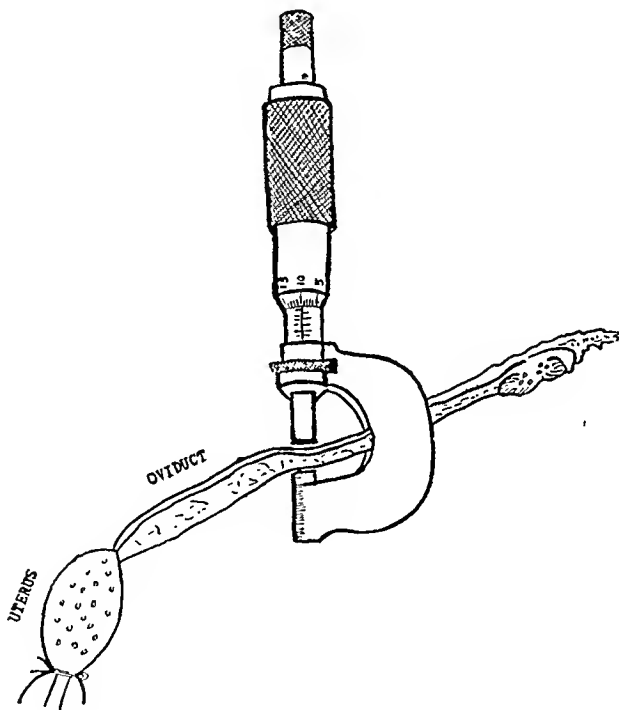


Fig. 2.—Micrometer clamp applied to the rabbit's oviduct.

In surviving extirpated uterus and tubes, it is possible to reproduce the contraction-relaxation phenomenon as observed during clinical insufflation. By immobilizing or constricting such Fallopian tubes, one can note the effect on the pattern of contractions. If the tubes (or one tube, the other being clamped off) are pinned down to a cork mat, the pins being inserted through the seromuscular edge thus preventing free motion, it will be seen that the rhythmic contractions disappear. If the pins are removed, the rhythmic contractions reappear, showing the passive part played by the uterus during the insufflation.

Artificial strictures of living and surviving tubes may be reproduced by applying clamps at any point of their course. This was accomplished in a number of living rabbits by means of a micrometric clamp gauged by notches to measure a thousandth of an inch (Figs. 2 and 3). It was used primarily to help in the calculation of the degree of stricture met clinically and determined by kymographic uterine insufflation. By

of pressure. The kymograph records both the pressure rise and fall. The CO_2 gas streaming through the Fallopian tubes acts as an elastic medium upon which muscle activity is recorded and in many instances, small, almost inaudible bubbles may be observed during the rise of pressure which is due to the fact that the tube lumen is not completely obliterated. The escaping bubbles under this circumstance are not squeezed out by the tubal contractions but by the driving force of the insufflating apparatus.

The number of oscillations is to a certain degree dependent upon the volume of gas transmitted through the tubes at a given rate. A certain amount of irritation due to increased pressure and possibly as a result of the CO_2 itself accompanies the rapid rate flow while very slow rates diminish the contraction relaxation rate. For this reason we have recommended a constant flow rate of 60 c.c. per minute for purposes of comparison in studying the effects of hormonal tubal contractility.^{10, 11}

The graphs obtained in clinical uterotubal insufflation either represent synchronous activity of both tubes or of the one tube which permits the CO_2 to pass through it at a lower pressure than it takes to pass through the other tube. I have frequently demonstrated this on the surviving and nonsurviving extirpated organs and also clinically as well as upon the manikin. The lumina of the tubes are not invariably equal and the tonicity also varies not infrequently, a fact recorded also by Whitelaw,¹² Randall,¹³ and Moequot and Palmer.¹⁴ Spastic muscle contractions may be produced by the galvanic current applied to the tube muscle, and if CO_2 is passing through the tube lumen a rise of pressure will be noted coincident with the blanching and constriction of the muscle. A similar effect was produced in the *Macacus rhesus* by pituitrin which by its oxytocic action either abolished the tubal contractions altogether for a few minutes or reduced their amplitude and frequency (A. H. Morse and I. C. Rubin¹¹).

Another clinical proof of the fact that rhythmic contractions as observed during uterotubal insufflation are due to the action of the tubal muscle is their complete absence or serious modification when the Fallopian tubes are adherent or strictured. The pathologic condition has been corroborated by many laparotomy observations. That no oscillations occur when both tubes are completely obstructed has already been mentioned. In this circumstance the tubes are paralyzed by the overdistention produced by the CO_2 gas proximal to the obstruction. If the obstruction is located at the uterine ends, the uterus becomes overdistended and fails to exhibit rhythmic contractions. If the tubes are adherent but incompletely obstructed, allowing the CO_2 to pass through the narrowed lumen, the rhythm is altered. The graph produced shows a higher initial pressure with a gradual sloping downward as the CO_2 passes through the constricted point. Depending upon the degree of stricture rhythmic fluctuations are either absent altogether or if present they are as a rule shallow and irregular, indicating the extent to which the tubal muscle has become pathologically altered and functionally impaired.

The clinical incidence of this tubal status with incomplete stenosis (stricture or adhesions) is considerable accounting for from 15 to 25 per cent of all sterility cases.

A clinical experimental demonstration of the fact that the pressure oscillations observed during uterotubal insufflation are conditioned by the action of the tubal muscle has been afforded in instances where temporary sterilization is accomplished by immobilizing the Fallopian

the uterine cavity. The pressure waves are therefore much reduced, practically neutralized in the siphon meter. This does not influence the pressure effects produced by the action of the tubal muscle because the amplitude of the latter is considerably greater than that of the uterus. Hence my departure in using aneroid manometers and other systems which have been of decided help in accomplishing results.

Although my conclusions regarding tubal contractility have been accepted by most workers, as for example Rucker,¹⁹ Mocquot, Palmer, Lejeune and Raizi,²⁰ Geist, Salmon and Mintz,²¹ Bernstein and Feresten,²² and S. Wimpfheimer,^{4, 5} who based their work on the original hypothesis, I have considered it worth while to reopen the question of tubal versus uterine contractions adding further clinical observations which have recently been made.

We have endeavored during the last two years to study uterine contractility apart from tubal contractility in women under different clinical circumstances: early stages of pregnancy including hydatid mole, dysmenorrhea, metrorrhagia with and without fibromyomas and in normal cases. The study has been facilitated by improvement in apparatus which has enabled us to carry out observations previously not possible.

As far as the tubes are concerned the rhythmic oscillations recorded on the kymograph during uterotubal insufflation by means of the siphon meter are actually in the main similar to those which are obtained when an aneroid manometer and photoelectric recorder are used. For small variations in pressure, the two last mentioned are more sensitive.

We have overcome the disadvantage of the siphon meter in studying uterine contractions by adopting an aneroid system with CO₂ as the medium in one apparatus (Grafax) and another using a fine pin valve (Foregger) in which the air chamber is reduced practically to zero. A third method utilizes a sensitive photoelectrical recorder with a water manometer which brings out the uterine action more graphically (Feitelberg).

These three systems have enabled us to demonstrate satisfactory motions of the uterus.* The media used were CO₂, saline solution, viscous ray opaque and hippuran injected into the free uterine cavity; and CO₂, air or saline within an intrauterine balloon.

To obtain graphs of the action of the uterine muscle the CO₂ is subjected to a pressure below that required for the gas to pass through the tubes. This is readily predetermined by testing the pressure necessary for the gas to pass through the uterotubal junction. If for example the initial pressure rise is 80 mm. Hg a pressure of not more than 50 or 60 mm. Hg will be maintained. The CO₂ within the uterine cavity serves the same purpose as air in an intrauterine balloon.

It will be noted from the tracings recorded when CO₂ gas is confined within the uterine cavity or is (encased) in the balloon or when salt solution is used (Figs. 4, 5, 6) that the type of contractions is similar in each case but that they differ materially from the pattern produced when CO₂ gas passes through the tubes. We have found that the uterus manifests contractility when distended by different media provided the

*The data obtained from the use of the newer apparatus will be presented in a separate paper by Drs. S. Feitelberg, A. Davids and myself.

means of such a clamp one gets an idea of the changes in the kymographic tracing produced by pathologic strictures encountered clinically. These vary from mild flattening out of the rhythmic oscillations to their complete disappearance. The results are similar in the living and surviving organs. Removal of the clamp is followed by restoration of the tubal motility.

As I have had occasion to observe previously, nonfunctioning Fallopian tubes as encountered in prolonged amenorrhea, fail to exhibit rhythmic contractions altogether or manifest occasional motions more or less weak. The low level of pressure, indicating poor muscle tone which is always present in such instances, distinguishes this condition from tubal strictures which are marked by high elevations of pressure.

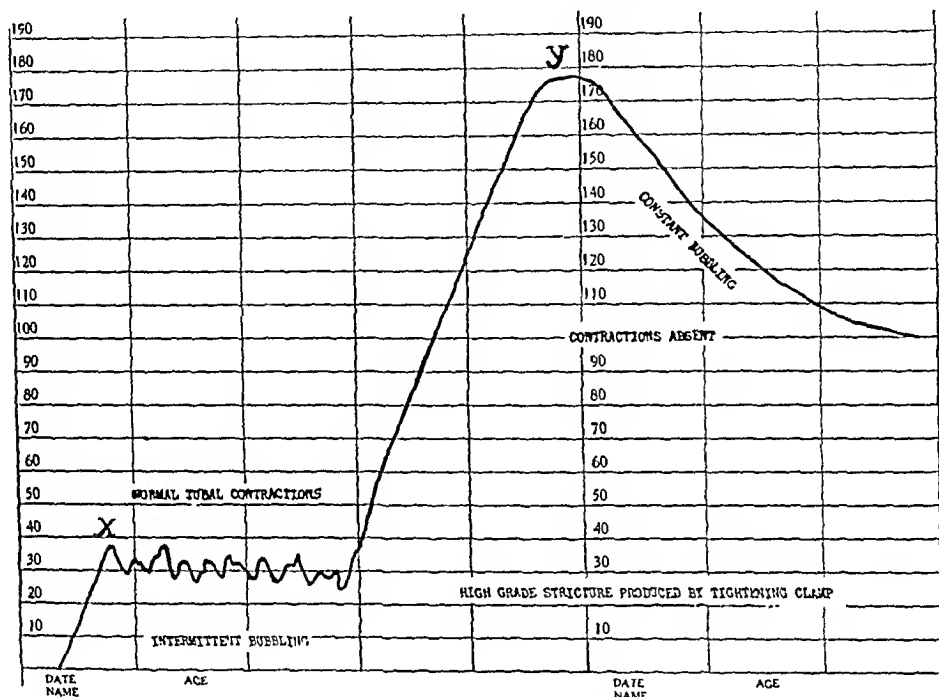


Fig. 3.—Showing the effect of constriction (stenosis) upon tubal contractility. Note pressure increase from 38 mm. Hg at X to 178 mm. Hg at Y after constriction and resultant abolition of contractions.

In 1927,² I stated that the rhythmic waves recorded on the kymograph during uterotubal insufflation are "not due to uterine contractions which in the nonpregnant state have so far not been demonstrated." Since then the literature abounds in reports upon uterine motility in the pregnant and nonpregnant state. The excellent work of C. Moir,¹⁵ S. R. M. Reynolds,¹⁶ of F. Falls,¹⁷ of F. L. Adair,¹⁸ and their collaborators is well known. Although my chief attention was focused upon tubal contractions, the possibility of demonstrating uterine motility by transuterine insufflation has been constantly in mind. The first step in this direction was the realization that the insufflation apparatus was not sensitive enough to record uterine changes. The water siphon meter contains an air chamber which dampens the registration of uterine motility. The air chamber of the siphon meter has a capacity much greater in proportion to the few cubic centimeters compressed within

degree of distention is not excessive. As there are 13 mm. of water to 1 mm. Hg the oscillations are magnified 13 times the size of the graph obtained by the mercurial manometer. The ink writer in the photoelectric recorder is controlled by a motor, hence the lag due to friction on the drum is much less than that produced by a floater. Whether uterine contractions are recorded by this apparatus or by an aneroid system, their force has been found in the nonpregnant state to average between $\frac{1}{3}$ and $\frac{1}{2}$ mm. Hg to $1\frac{1}{2}$ mm. Hg as compared to a range of 30:40 mm. Hg exhibited by the tubes. They are also less frequent per minute.

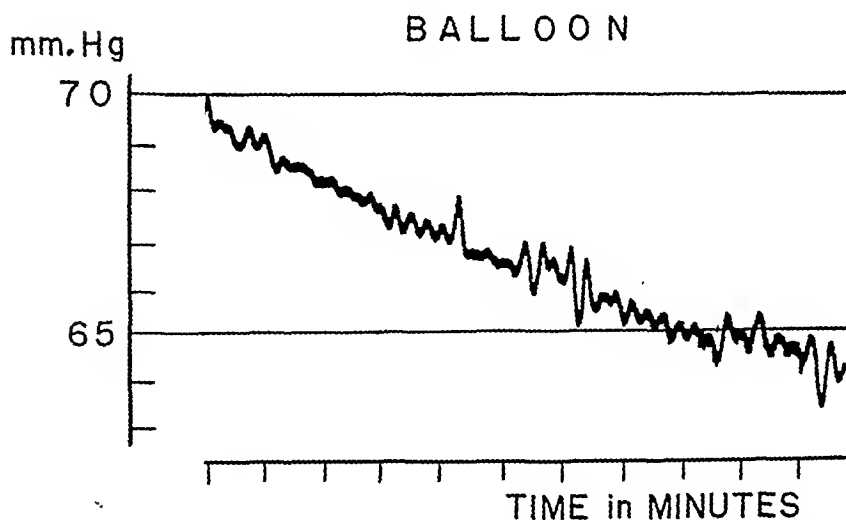
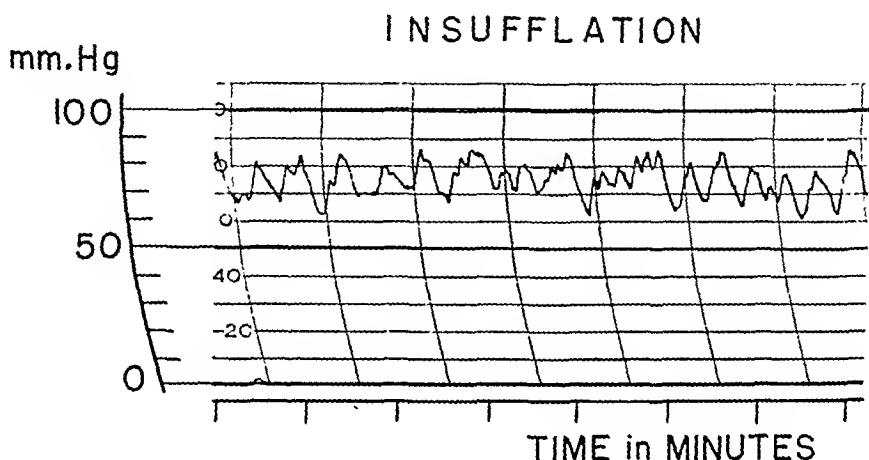


Fig. 6.—Showing contrast between amplitude of oscillations produced by tubal contractions recorded by an aneroid manometer (Grafax) and the very shallow oscillations produced by uterine contractions recorded by means of an intrauterine balloon. (Photoelectric recorder.)

When solutions are used, the intrauterine pressure is carefully noted avoiding pressures which would force the fluid through the tubes. This is readily determined previously by insufflating with CO_2 in order to note the level at which the CO_2 gas passes from the uterus into and through the tubes. However, as a further check the pelvic organs were exposed to x-rays and films were taken at various points of the injection.

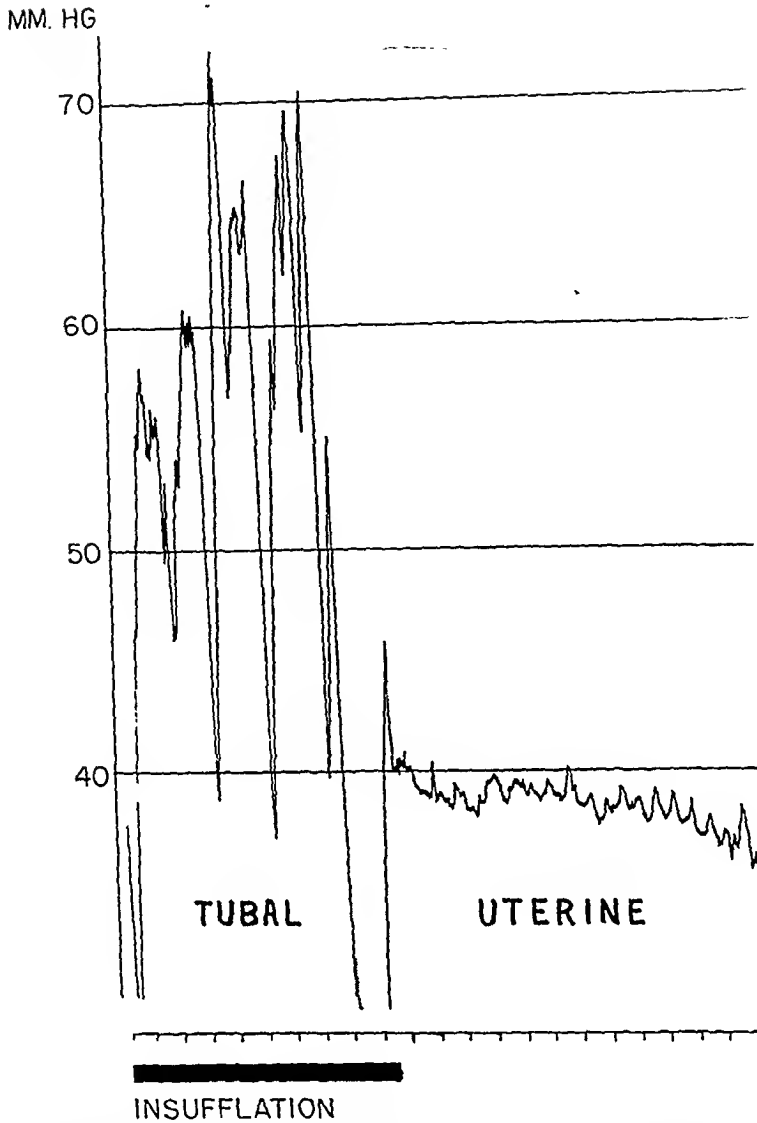


Fig. 4.—Note that the amplitude of uterine contractions varies between $\frac{1}{2}$ mm. Hg and 2 mm. Hg (Grafax insufflation apparatus) whereas the amplitude of tubal contractions ranges between 10 mm. Hg and 20 mm. Hg (photoelectric recorder).

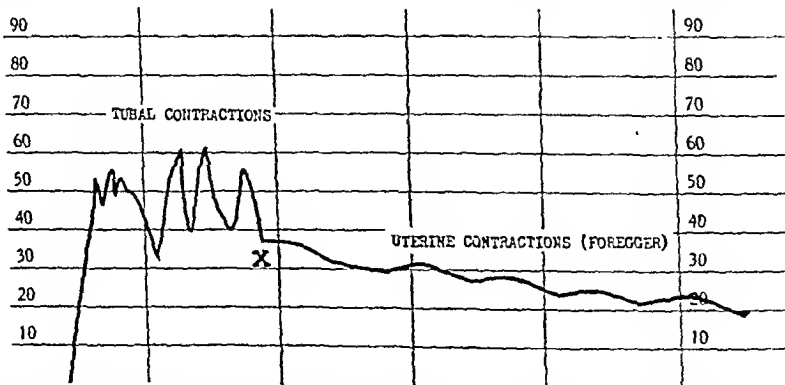


Fig. 5.—The contrast is just as striking between the tubal and uterine contractions when the CO_2 gas flow is stopped, X, and the uterine cavity contains CO_2 only at a pressure of 35 mm. Hg. (Foregger apparatus.)

10 cases, contractility was absent in four (one cancer; two metropathias; one hypoplasia with sterility); weak in four (two metrorrhagia of probably ovarian origin; one hypoplasia with amenorrhea; one uterus subnormal probably due to hypofolliculinization); strong in two cases (one fibroma; one abortion). Even in the cases where the contraction has been marked, it was not produced before a pressure of 4 cm. of mercury.

The number of cases upon which Moequot has based his conclusions and of my own cases in this respect is not large enough for statistical purposes. As far as it goes the same general law applies to pathologic uteri as for pathologic Fallopian tubes, namely that their contractility is either lost altogether or becomes more or less reduced.

Summary

Recent clinical observations and experimental work on living and surviving genital organs of the rabbit by means of kymographic uterotubal insufflation have confirmed earlier conclusions.

The kymograph tracings of manometric oscillations observed during uterotubal insufflation represent rhythmic tubal contractions and relaxations. They are not due to changes in tonicity per se but to actual contractions whose rate varies per minute in accordance most probably with the particular phase of the ovulation menstruation cycle. The non-pregnant uterus has been demonstrated to exhibit a contraction relaxation phenomenon under suitable distention and recorded by appropriate manometric devices. The character of the contractions differs in each organ, the uterus in general undergoing slower motions of much shallower force. The pressure medium in the uterus may be solutions, gas or air without balloon enclosure and with an intrauterine balloon. The ideal pressure medium within the lumen of the tubes has been found to be CO₂ gas which is insufflated at a constant rate of flow. Salt solution or other fluid injected through the tubes under a constant pressure rate flow has been found unsuited in comparison with CO₂ in the present set-up for the recording of pressure oscillations emanating from the tubes. Adoption of aneroid manometers and a photoelectric recorder has helped in establishing the difference in pattern between tubal and uterine contractions in the same and different cases.

I wish to express my appreciation for cooperation in this study to Dr. S. Feitelberg, physicist to Mt. Sinai Hospital, and Dr. Arthur M. Davids; and also to Mrs. Carl Pforzheimer, Jr., who rendered valuable technical assistance.

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Hippuran was used for this purpose and appeared to have no appreciable influence over the character of the uterine contractions as previously elicited by sterile saline solution. The solution was injected in a uniform pressure rate flow by the force of CO_2 gas from the insufflating apparatus (Fig. 7). X-ray visualization of the tubes was thus made possible at a rate comparable to the flow of CO_2 gas which gave the opportunity to observe whether and to what extent tubal motions were demonstrable by their effect upon the column of fluid. These motions are extremely superficial when a viscous contrast medium is used.

Although uterine contractions may be thus best studied in cases where both tubes had been removed comparing the results with balloon experiments and the results obtained in cases having intact Fallopian tubes, it was considered desirable to compare the results in the same case where tubal contractions could be elicited apart from uterine contractions. This was carried out in a number of instances.

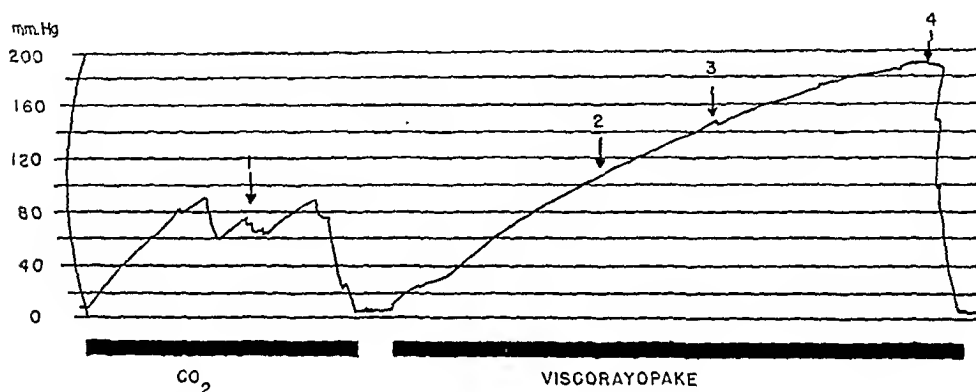


Fig. 7.—Kymographic tracing of uterotubal insufflation with CO_2 contrasted to that obtained by injection of a viscous ray opaque contrast medium at the same rate flow.

In a most recent experiment, the uterus and tubes were insufflated in the usual way. The graph thus obtained served for comparison. Following this procedure the parametria were injected with 1 per cent novocain solution. It could not be predicted to what degree the character of the contractions would be changed nor whether the uterus was completely paralyzed and with it possibly the tubes. The method of injection obviously includes the possibility of affecting the innervation of the tubes as well as of that of the uterus. That uterine or tubal motions are not dependent entirely upon nervous influences has been demonstrated upon the surviving extirpated organs. However, the infiltration was intended to produce a mechanical barrier which should in any event inhibit the motion of the myometrium.

Although the novocain infiltration could not be exclusively limited to the myometrium and parametrium leaving the mesosalpinx free, the result of this one experiment demonstrated that despite complete loss of motion in the uterine muscle the tubes may retain more or less the same power of contractions as they exhibited during uterotubal insufflation before the parametria were infiltrated with the novocain solution.

Moequet has insisted for a long time and his hysterographic observations with lipiodol under manometric control using low pressures appear to corroborate his contention that: the great majority of pathologic uteri have either a much diminished contractility or none. In their

HYDATIDIFORM MOLE AND ASSOCIATED TUMORS OF THE CHORION*

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THE introduction of the biologic tests for gonadotropic substances in the urine, which are strongly positive in instances of abnormal chorionic activity, has stimulated a renewed interest in disturbances of the chorion. The literature in recent years contains numerous articles dealing with various phases of the subject, some of which present an optimism which hardly seems justified in view of the past experiences with this bizarre group of disorders. The most common of the diseases of the chorion is hydatidiform mole. Whether hydatidiform mole is primarily a neoplastic or a degenerative process still seems unsettled. Virchow believed that the process was essentially a myxomatous degeneration of the connective tissue of the chorionic villi, and designated it as myxoma chorii. Recently Hertig¹ after a rather extensive study also suggests that the degenerative process is primary and that the epithelial proliferation is secondary to the degenerative changes. In 1895 Marehand² pointed out that the essential feature was an irregular and profuse proliferation of the chorionic epithelium, and it still seems to be generally accepted that the proliferative changes are the primary lesions.

The diagnosis of a hydatidiform mole in the uterus before the passage of some of the vesicles is often difficult, but occasionally can be accomplished. The most significant symptom in our experience has been a slight but persistent dark bloody discharge from the uterus. In one instance the diagnosis was made in a patient with such a history, who was presumed to have a threatened abortion, but who developed, while under observation, bilateral cystic ovaries. In another case the diagnosis was made in an instance of presumed pregnancy, from the history of slight persistent vaginal bleeding and the presence of ovarian cystomas. The absence of fetal outlines by x-ray examination in those cases in which the uterus is as large as or larger than a sixteen weeks' pregnancy, practically establishes the diagnosis. Disproportion between the size of the uterus and the duration of the presumed pregnancy is a helpful sign when present, but this discrepancy is not always present, and in a few of our cases the uterus was actually smaller than was anticipated for the duration of the pregnancy. The presence of large amounts of gonado-

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911 PARK AVENUE

Discussion

DR. M. PIERCE RUCKER, RICHMOND, VA.—The question Dr. Rubin proposes is not whether the nonpregnant uterus contracts or whether the tubes contract, but what causes the waves encountered during an insufflation of normal tubes. What the pen on the manometer records is the pressure of the CO₂. If the gas is flowing at a constant pressure, the wavelike variations in the record can be caused only by variations in the outflow. The most logical place to look for this variation in the outflow is in the narrowest part of the system, i.e., the tubes. The situation is very much like a millpond with a constant stream feeding the pond. To vary the "head" of water you put more or less obstruction in the mill race. The same amount of obstruction in the pond itself would have no effect whatever.

It seems to me that Dr. Rubin had already proved conclusively that the waves are due to tubal contractions. He now proves that they are due to the contraction of the narrowest part of the tube. The fact that you get no waves when the tubes are closed would indicate that the contractions of the uterus have nothing to do with it. He has also shown with extirpated organs that the fall in pressure coincides with relaxation of the tubes, and a rise with the contraction of the tubes.

One point only touched upon is that the contraction of neither uterus nor tubes is powerful enough to be shown working against a pressure of from 60 to 110 mm. of Hg or to be recorded when there is so much compressible gas in the tubing. When Knauss' work first came out I tried to repeat it with an ordinary Rubin apparatus but failed completely. In fact, the only time I have been able to record contractions of a nonpregnant uterus was when the recording system was entirely filled with water.

The fact that diseased tubes may be patent but show no waves of contraction and relaxation is an important clinical observation. When such tubes are found in the course of a sterility study, treatment with foreign protein injections, or with heat, will frequently restore them to a normal condition and the waves will appear in the kymographie record.

I note that Dr. Rubin is investigating contractions of the nonpregnant uterus, and I look forward to seeing this phase of his work appear more in detail.

DR. RUBIN (closing).—Those shallow uterine contractions that we see in the nonpregnant state range between a millimeter and a millimeter and one-half of mercury, and are tremendously intensified in the pregnant state. We have had occasion to observe this wide range in fluctuations with the photoelectric recorder in cases of second and third months of pregnancy in a number of instances before inducing a therapeutic abortion.

area was excised. A Friedman test was still strongly positive one month after operation. A course of x-ray therapy was given over the pelvis, and two weeks later the Friedman test was negative. The Friedman test has remained negative, and the patient has now survived for nine years.



Fig. 1.—Mrs. P. (Case 60215). Chorionic villus, Langhans' cells, and syncytium in uterine wall. $\times 50$.

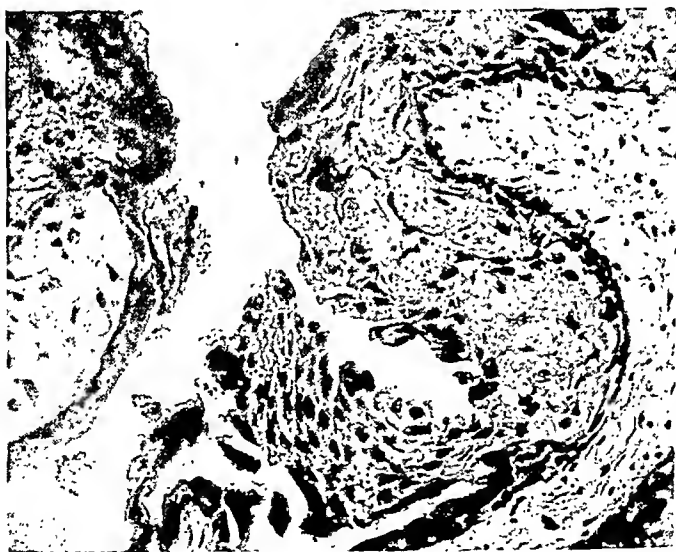


Fig. 2.—Mrs. P. (Case 60215). High power of an area in Fig. 1, showing villus and Langhans' cells and syncytium. $\times 240$.

CASE 2.—(No. 130279.) Mrs. J. H. K., a 24-year-old white woman, had her last menstrual period Nov. 7, 1936. A slight bloody discharge had been present since December, while moderate bleeding had been present since March 5, 1937. She was admitted to the hospital on March 15, when examination showed the uterus to be the size of a four months' pregnancy, with a cystic mass palpable to the right of the uterus. An x-ray picture showed no evidence of a fetal skeleton. With a tentative

tropic substances in the urine in cases of mole has led to attempts to establish the diagnosis by quantitative determinations while recently gonadotropins have been found in the spinal fluid in cases of hydatidiform mole.

The majority of hydatidiform moles are either spontaneously passed or may be removed through the vagina. Some cases, particularly those in the older age group in whom the diagnosis is established before the passage of vesicles, may be more satisfactorily managed by hysterectomy. The manner of removing the mole requires an individualization of each patient. An important part in the treatment is the subsequent examinations of the patient including tests for urinary gonadotropin.

Many instances of hydatidiform mole are definitely benign, and following their passage no serious sequelae develop, while others show a marked tendency to proliferation and to invasion of the uterine and pelvic blood vessels, often with metastatic nodules in the uterine and vaginal walls, so that the mole is considered as malignant or destructive. For this group Ewing³ proposed the term *chorioadenoma destruens*. Others imply that there is but little justification for this term, and prefer to consider the malignant type of mole simply as a milder variant of chorion-epithelioma. Our attempts to distinguish between a benign and malignant mole by examination of the vesicular material which is passed, have been fruitless, and we are unable to predict from the gross and microscopic examination of the vesicular material which of the moles have already invaded the pelvic tissues or which ones will subsequently be followed by invasive chorionic cells. However, some believe that the malignant types show either an invasion of the stroma of the villi with epithelial elements, anaplasia of the epithelium, or chorioepithelial elements growing detached from the villous structures. After removal of the uterus, we have classified some of our cases as malignant moles or chorioadenomas because of marked proliferation of Langhans' cells and syncytium, and local extension, but with preservation of villous outlines. Two of these seem of sufficient interest to justify a brief synopsis of their records.

CASE 1.—(No. 60215.) Mrs. P., a 49-year-old white woman, who had had three previous pregnancies, had the last normal menstrual period in August. Some vaginal bleeding began in October and continued until her admission to the hospital in December. Examination showed, in addition to an enlarged softened uterus, a firm nontender mass the size of a walnut on the anterior vaginal wall just to the left of the urethra. On a presumptive diagnosis of hydatidiform mole, a hysterectomy and a bilateral salpingo-oophorectomy were performed. A microscopic diagnosis of chorioadenoma was made because of the rather extensive invasion of the uterine wall by syncytium and Langhans' cells. On the second postoperative day vaginal bleeding occurred, and an examination showed it to be arising from the nodule in the vagina, which had apparently eroded through the mucosal surface. Tissue from the nodule revealed chorionic villi and proliferating Langhans' cells. The cystic

and filled with mucoid material. Pathologic examination showed villous structures and chorionic cells invading the veins of the uterus. Lutein cysts were present in both ovaries. One month later the Friedman test was still strongly positive, and 8,000 r. of x-ray therapy were given over the pelvis through four portals. X-ray pictures of the chest were negative and the pelvis and vagina were free. Six months after operation and five months after radiation the Friedman test was negative for the first time. Four months later, ten months after operation, in spite of normal chest and pelvis, the Friedman became positive again, and remained positive for ten months. One year later (January, 1940) the test became negative and has remained negative and the patient remains well.



Fig. 5.—Mrs. D. J. T. (Case 110100). Gross specimen showing mass of tissue on posterior uterine wall. Bilateral lutein cysts.

A syncytial infiltration of the uterine wall with an associated inflammatory reaction may occur, a condition commonly spoken of as syncytial endometritis, although originally described as an atypical chorionepithelioma. Its designation as a tumor is open to question, although at times the uterus is enlarged and infiltrated by a bulky mass with neoplastic characteristics, in which case it is spoken of as syncytioma. In these conditions it is assumed that no Langhans' cells are present but only syncytium. The following case is one of this nature.

CASE 3.—(No. 110100.) Mrs. D. J. T., a 19-year-old white woman, who in 1934 had eclampsia, was admitted in October, 1938, with the uterus

diagnosis of hydatidiform mole and a lutein cystoma of the right ovary, a bougie was inserted in the uterus, and a mole evacuated twelve hours later. Two months later the Friedman was strongly positive, although the right ovary seemed to be decreasing in size. A curettage was done,

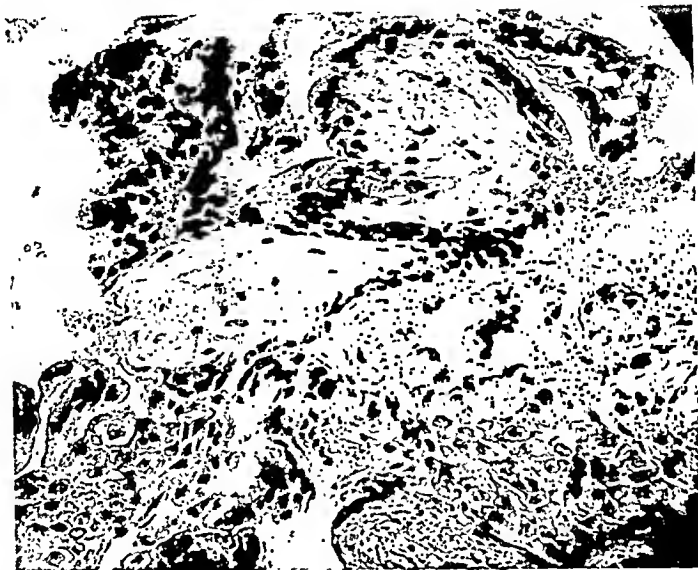


Fig. 3.—Mrs. P. (Case 60215). Section from vaginal nodule. Chorionic villi, Langhans' cells, and syncytium. $\times 57$.

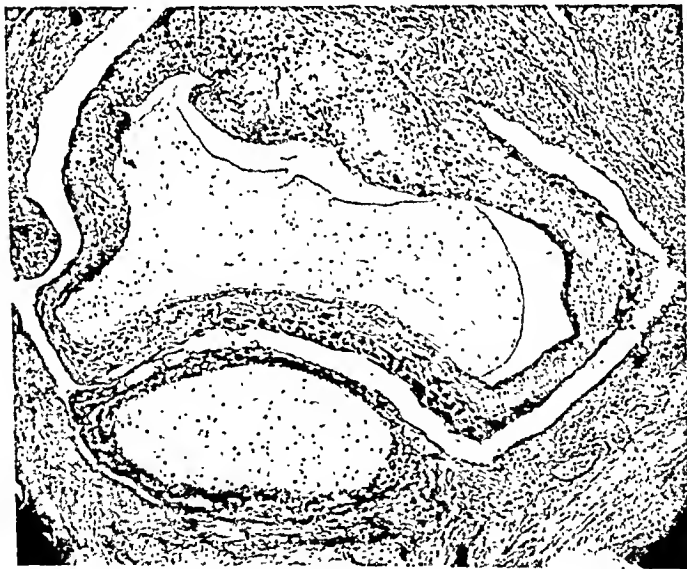


Fig. 4.—Mrs. J. H. K. (Case 130279). Section from uterine wall showing vein containing chorionic villi and Langhans' cells. $\times 55$.

the tissue revealing only an endometritis with a decidual reaction. One month later, three months after the passage of the mole, the Friedman was still strongly positive, so that on a presumptive diagnosis of chorion-epithelioma, a hysterectomy and a bilateral salpingo-oophorectomy were done. At the time of operation masses of mucoid material were present in the right broad ligament, and the right uterine vein was distended

some vaginal bleeding until admission to the hospital on Feb. 12, 1936. During the three months prior to admission two curettages were done by her local physician to control the bleeding. Examination revealed an apparently normal sized uterus with a similar-sized mass to the right which was thought to be an ovarian cyst. A Friedman test was strongly positive. A preliminary curettage was attempted, but the uterine sound met no obstruction beyond the cervix, so that a diagnosis of instrumental perforation of the uterus was made. On exploration through an abdominal incision, a bicornuate uterus with an old perforation between the two horns and a small submucous fibromyoma in one horn was found. Hysterectomy and bilateral salpingo-oophorectomy were done. A rather careful gross and microscopic examination of the structures removed failed to reveal any chorionic tissues, and no lutein cysts were found in the ovaries, the only one of our cases in which they were not found on microscopical examination. Three weeks following operation, the Friedman was still positive, but was negative in six weeks, has remained negative since, and the patient remains well.

TABLE I. PATIENTS WITH HYDATIDIFORM MOLE AND ASSOCIATED TUMORS

CASE	AGE	CONDITION	REMARKS	RESULT
1	19	Mole	Vaginal delivery, followed for only 7 months	Well?
2	27	Mole	Vaginal delivery	Well
3	27	Mole	Vaginal delivery	Well
4	45	Mole	Vaginal delivery	Well
5	18	Mole	Vaginal delivery	Well
6	19	Mole	Vaginal delivery	Well
7	21	Mole	Toxemia, vaginal delivery	Well
8	20	Mole	Vaginal delivery, pregnancy 2 years later with eclampsia	Well
9	15	Mole	Vaginal delivery, normal pregnancy 1 year later	Well
10	20	Mole	Vaginal delivery, normal pregnancy 2 years later	Well
11	30	Mole	Vaginal delivery, normal pregnancy 4 years later	Well
12	22	Mole	Vaginal delivery, D. and C., syncytial endometritis	Well
13	30	Mole	Vaginal delivery, positive Friedman 3 mo. later; D. and C. Normal pregnancy removed, uneventful pregnancy 2 years later	Well
14	51	Mole	Hysterectomy	Well
15	26	Mole	Hysterectomy	Well
16	26	Mole	Hysterectomy, twisted lutein cyst	Well
17	49	Mole	Vaginal metastases (excision), hysterectomy, radiation	Well
18	19	Mole	Toxemia, vaginal delivery, syncytioma, hysterectomy	Well
19	34	Mole	Vaginal delivery, syncytioma, hysterectomy	Well
20	43	Mole	Vaginal delivery, syncytioma, hysterectomy	Well
21	24	Mole	Vaginal delivery, chorioadenoma, hysterectomy	Well
22	26	Mole	Chorionepithelioma of broad ligament 1 year later. Inoperable, radiation, pulmonary metastases	Death
23	35	Mole	Chorionepithelioma 3 mo. later, hysterectomy, 1 month later brain metastases	Death
24	19	Mole	Exploration and biopsy 6 mo. later. Inoperable chorionepithelioma. Death assumed	Death
25	23	Primary chorionepithelioma of tube, hysterectomy, radiation, brain metastasis		Death
26	36	Positive Friedman and bleeding after normal pregnancy. D. & C., perforated double uterus, hysterectomy, no chorionic tissue		Well

In another patient, who had passed a mole in June 1939, the Friedman was still positive and the uterus slightly enlarged three months later. A

the size of a five months' pregnancy with hypertension, albuminuria, and edema. Eight days after admission, a mole was spontaneously passed from the uterus with profuse hemorrhage requiring massive transfusions. After passage of the mole, a large cyst was found filling the pelvis. One month later (December, 1938) the Friedman was negative, although orange-sized bilateral ovarian cysts were present. One month later (January, 1939) the Friedman was positive again, some abnormal uterine bleeding was present, the uterus was enlarged to about twice the normal size, and the cysts seemed larger than at the time of the previous examination. An x-ray of the chest was normal. Hysterectomy and bilateral salpingo-oophorectomy were done. The pathologic diagnosis was syncytioma and lutein cysts. Two weeks later the Friedman was negative, has remained negative, and the patient remains well.

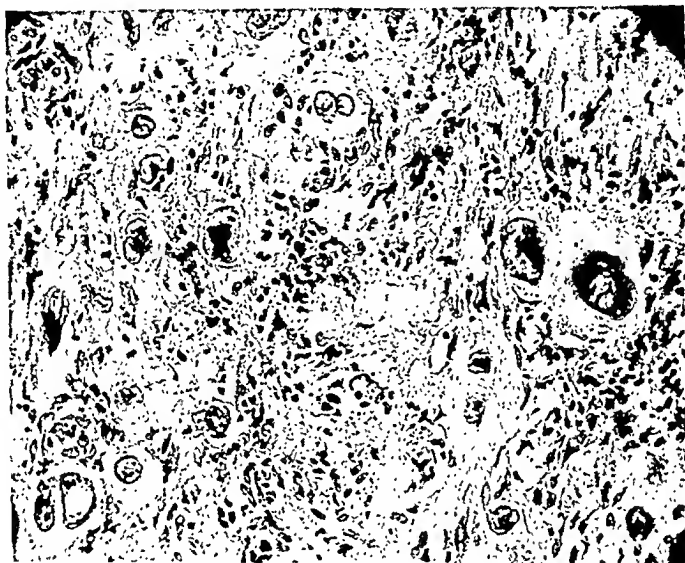


Fig. 6.—Mrs. D. J. T. (Case 110100). Section through mass in posterior uterine wall showing syncytial cells. $\times 57$.

We reserve the term chorionepithelioma for the highly malignant tumor, consisting of a disorderly growth of both Langhans' cells and syncytium with an absence of villous formation. The growing masses of tumor cells splits the uterine muscle with destruction of tissue, necrosis, and hemorrhage, invades the sinuses, and is characterized by widespread metastases, particularly to the lungs and brain. We feel that this is a highly fatal tumor, and the four cases of this type in our records have all died. Fortunately this very malignant type seems to be rare. Of the four cases in our series three followed the passage of moles, while one was a primary chorionepithelioma of the Fallopian tube, which has been previously reported.⁴

We have had in following patients, with Friedman tests, after pregnancies or moles, two cases of passing interest.

CASE 4.—(No. 121613.) Mrs. E. T., a 36-year-old white woman, was delivered at full term on Nov. 3, 1935, since which time there had been

present in excessive amounts in the urine and apparently also in the spinal fluid in instances of chorionic growths. The presence of a positive test indicates the presence of viable chorionic tissues, but the frequency with which the test becomes negative and then subsequently positive, indicates that too much reliance should not be placed on a single negative test. The presence of a persistent positive test following a mole, abortion, or pregnancy justifies the diagnosis of persistent viable chorionic cells, although in one of our cases with bleeding and a positive test three months post partum, no chorionic tissue was identified in the uterus, tubes, or ovaries. It is quite likely that a small nest of cells was overlooked, although many sections were taken. In another instance, another pregnancy had supervened within three months of the passage of a mole, and although its possibility was considered, we were reluctant to rely upon it. While curettage is often helpful and is commonly used in the follow-up of these patients, negative findings may be entirely misleading, and the procedure is not without danger. Obviously the curette will not obtain tissue from masses outside of the uterine cavity, which is a rather common situation.

The problem, which always presents itself, is what course to pursue in the presence of a persistent positive test following the passage of a mole, an abortion, or term pregnancy. While we are justified in assuming the presence of chorionic tissue, are we justified in radical operative procedures on the assumption that a chorionepithelioma is present? We have perhaps erred on the radical side, but the hope of removing or preventing a chorionepithelioma has possibly justified our course. This course has in our hands resulted in radical procedures for chorioadenomas and syncytiomas, the termination of a normal pregnancy, and in one case the inability to find any chorionic tissues in the removed structures. It is our custom in the presence of a persistent positive test to perform a curettage, and if a month or so later the test is still positive, we believe that an abdominal exploration of the pelvis with hysterectomy is advisable.

The question arises whether apparently benign chorionic tissues remaining in the uterine walls and the vessels of the uterus and pelvis may not subsequently assume malignant characteristics. The same consideration arises in regard to deported chorionic tissue (deportation of chorionic villi). Apparently the question cannot be answered with certainty, but one is inclined to believe that they may. This would explain the presence of metastatic lesions with an absence of any primary malignant lesion in the uterus. One of our cases of chorionepithelioma manifested itself as a hemorrhagic mass in the right broad ligament one year after an early abortion with vesicular villi. At abdominal exploration the uterus was small and separate from the mass. The mass in the right broad ligament was inoperable and was treated by radiation. The patient, however, died of pulmonary metastases shortly after the radia-

curettage was performed and a normal pregnancy removed from the uterus. The patient has since passed through a normal pregnancy and an uneventful delivery.

We have records of 24 patients who passed moles, and in addition one patient with a primary chorionepithelioma of the Fallopian tube, and one case of a persistent positive Friedman with uterine bleeding for three months after a normal pregnancy. Of the 24 patients with moles, 4 had them removed by hysterectomy and 20 passed them through the vagina. Thirteen of the 20 whose moles were delivered through the vagina had an uneventful recovery, although one of the patients in a subsequent pregnancy had a spontaneous rupture of the uterus, probably from a weak spot in the uterine wall as a result of invasion of the wall with chorionic tissue. Curettage in this patient two weeks after passage of the mole produced a large quantity of tissue, which was diagnosed as syncytial endometritis. Four of the 20, who were delivered through the vagina, had positive Friedman's tests following the moles and were treated by hysterectomy, one diagnosed as chorioadenoma and three as syncytioma. All of these patients have survived. The other three who passed the moles through the vagina developed chorionepithelioma, all of them occurring before the use of the biologic tests in the subsequent examination and observation of patients who have passed moles. The patients who had a diagnosis of chorionepithelioma died.

TABLE II. ANALYSIS OF CASES

	NUMBER
Moles passed through vagina, uneventful recovery	13
Moles delivered by hysterectomy, uneventful recovery	4
Moles passed, positive Friedman, hysterectomy	
Chorioadenoma	1
Syncytioma	3
Moles passed, subsequent chorionepithelioma	3
Primary chorionepithelioma of tube	1
Positive Friedman and bleeding 3 mo. following normal pregnancy and delivery. No chorionic tissue found	1
Total	26

TABLE III. HYDATIDIFORM MOLES

	NUMBER	PER CENT
Delivered by hysterectomy	4	16.7
Vaginal delivery, uneventful recovery	13	54.2
Vaginal delivery followed by chorioadenoma	1	4.1
Vaginal delivery followed by syncytioma	3	12.5
Vaginal delivery followed by chorionepithelioma	3	12.5
Total	24	100.0

Discussion

One of the most interesting developments in the consideration of chorionic growths is the use of the biologic tests for urinary gonadotropic substances in the diagnosis and prognosis. These hormones are often

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Discussion

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—After a patient has been delivered of an hydatidiform mole, what is the best means of detecting, at the earliest possible moment, the development of chorionepithelioma? Since the histologic picture presented by hydatidiform mole is often unreliable as a prognostic guide and since clinical phenomena may be misleading, Dr. Williams rightly emphasizes the importance of endocrine observations in following these patients. But, as he points out, here also pitfalls await us. Occasionally, the test may become negative, turn positive again, and later show once more a negative reaction. We have observed this in one of our cases, as have others. Moreover, Schumann has reported a case in which a chorionepithelioma developed six months after a supposed miscarriage although repeated hormonal tests in the interim had been negative. Others have reported bizarre and irreconcilable results of a similar character.

But even if it be granted that hormonal tests have been misleading in occasional instances of this disorder, it must also be admitted that in most cases they follow a definite pattern and are of great value. It would seem desirable, therefore, to look carefully into this question and ask if there is any way in which endocrine studies can be made to serve our purpose more reliably than they have at times in the past. That serum gonadotropin does follow a definite pattern following the expulsion of an hydatidiform mole in the average case is shown by the studies of Brindeau, Hinglais, and Hinglais. Basing their statements on 86 cases, they found that their patients fell into three main groups. In Group I, the serum gonadotropin fell rapidly to zero within two or three weeks; in Group II, it disappeared slowly, the mean time of disappearance in this group being almost eight weeks; there was great variability, however, and in 3 cases small amounts of gonadotropin were still present in the serum after three months; in Group III, the serum gonadotropin decreased for a few weeks and then showed a sudden upturn. The moles in Group I and II were all benign, as shown by the subsequent clinical course, while the patients in Group III developed chorionepithelioma. The authors, therefore, lay great stress on the secondary upward swing of gonadotropin, but this can only be demonstrated, of course, by quantitative assay.

Dr. Eleanor Delfs of our Clinic has had the opportunity of following one case of hydatidiform mole with quantitative serum gonadotropin assays with results which are shown in Table I. At the time of expulsion of the mole, the concentration

TABLE I. SERUM GONADOTROPIN* FOLLOWING DELIVERY OF HYDATID MOLE

Case E. McK.—188903

Day	½	11	20	29	36	43	50	64	78	106
Units/L	515,000	12,000	11,600	2,600	570	350	225	0	0	0

*International standard units of chorionic gonadotropin.

of the hormone in the serum was very high, a half-million units per liter, but this fell rapidly to reach 2,600 units by the twenty-ninth day. This patient still showed serum hormone levels between 200 and 500 units between the thirty-sixth and fiftieth day, and it should be pointed out particularly that these lower levels might or might not have given a positive Friedman reaction, depending upon the concentration of the urine, the condition of the rabbit, etc. In other words, it is conceivable that we

tion. Occurrences of this nature suggest that chorionic tissue remaining either inside or outside of the uterus may eventually assume malignant qualities. If this contention is correct then probably a radical method of treatment is justified in those cases in which chorionic tissue remains in the pelvis, invading uterine walls and vessels, whether we call them benign or malignant moles, chorioadenomas, syncytiomas, or milder variants of chorionepitheliomas.

The presence at times of lutein cysts in the ovaries in association with chorionic growths has long been recognized, and their general tendency to retrogress following the passage of a hydatidiform mole is well known. Their frequency as reported in the literature seems to be dependent upon them being of sufficient size to permit detection on physical examination. In some cases, however, they are not sufficiently large to be definitely palpated on bimanual examination. They have been found microscopically in all of our cases in which the ovaries were removed and in which chorionic tissues were present in the pelvis, although in some the ovaries were not sufficiently enlarged to detect them on vaginal and abdominal examination. In two of our cases the cysts had partially twisted on their pedicles and gave rise to sufficient symptoms to require their removal.

Our experience, with these chorionic tissues which persist in the pelvis after the passage of a mole, suggests that the prognosis varies with the presence or absence of villous structures and with the presence or absence of proliferating Langhans' cells. All patients in our cases which we have classified as benign hydatidiform mole, malignant mole or chorioadenoma, and syncytioma have survived, while those in cases classified as chorionepithelioma, masses of Langhans' cells and syncytium without villi, have died. If this is generally true it might seem to justify an attempt to classify them on some such basis as that proposed by Ewing.³

Summary

A discussion of hydatidiform moles and their subsequent course with a review of 24 cases is presented. The mole may be benign, its passage complete and recovery may be uneventful. In others, approximately one-half of our cases, chorionic tissues remain in the uterine cavity or in the uterine walls, and cause persistent positive biologic pregnancy tests.

We have classified these cases microscopically as syncytial endometritis or syncytioma (infiltration with syncytium only), malignant mole or chorioadenoma (syncytium, Langhans' cells and villi), or chorionepithelioma (Langhans' cells and syncytium).

Those diagnosed on this basis as chorionepithelioma have died, while all of the others have survived.

I wish to express my appreciation to Dr. James R. Cash and to the other members of the Department of Pathology, for the pathologic studies and for invaluable aid and suggestions in the preparation of this material. I am indebted to Dr. J. R. Cash of the Department of Pathology and to Dr. J. R. Knight of the Department of Obstetrics and Gynecology for the preparation of the photomicrographs.

tion of such cases chorionepithelioma will not be found. Instead of this, one will often discover that the chorionic hormone production has been kept up by incompletely removed but benign hydatidiform mole. In many cases the molar tissue is actually irremovable by curettage, because it may have penetrated deeply into the maternal vascular channels. This was true, for example, in one of the patients included in Dr. Williams' series whom I had the opportunity, through his kindness, of observing with him, and I have had similar experiences with a number of other patients.

DR. FOSTER S. KELLOGG, BOSTON, MASS.—Is there any validity in the theory that an immediate study of the mole material will give an indication as to whether that mole will become malignant? Our pathologist at the Boston Lying-in Hospital is of the opinion from his work that, at least in a certain number of instances, he is able from the frozen sections to say that the mole is potentially malignant and that hysterectomy at that time is justified on this basis.

DR. GEORGE M. SHIPTON, PITTSFIELD, MASS.—We have had the disappointing experience of being mistaken on the Friedman test in the diagnosis of an ordinary pregnancy. Of course, it is generally accepted that there is a 5 per cent error and for that reason many people do two rabbit tests instead of making a single test. I would like to ask just how many rabbits were used in the tests which he refers to as negatives that should not have existed as negatives?

DR. WILLIAMS (closing).—Dr. Eastman's suggestion in regard to quantitative serum determinations seems to be of real value. With the facilities available to us, however, we have been unable to make these determinations.

In answer to Dr. Kellogg's question regarding the diagnosis by examination of the vesicular material passed, all I can say is that we have been unable to determine whether or not it has malignant potentialities or whether masses of chorionic tissue remain in the vessels and walls of the uterus.

Dr. Shipton raised the question of the number of tests which were made. While we have simply stated that a Friedman was negative or positive, these have been on the basis of repeated tests. Several are usually done before any radical procedure is considered in a young woman.

might have obtained a negative Friedman reaction on the thirty-sixth day, a positive one on the forty-third day, and again a negative response on the fiftieth day, despite the fact that the serum hormone concentration was decreasing in a smooth and normal manner. Only quantitative assays can give clear-cut evidence of this progressive decrease. Likewise, in the series of Brindeau, Hinglais, and Hinglais, a small fraction of their cases continued to show small amounts of hormone in the serum for three to five months, borderline amounts which might or might not have given a positive Friedman, depending on the circumstances mentioned above.

It would thus appear that the Friedman test, although of the utmost value in the diagnosis of pregnancy, is not sufficiently delicate to reveal accurately the progressive decrease in gonadotropin which follows the expulsion of benign moles. Accordingly, the gist of my discussion is to suggest the employment of quantitative assays on the serum in following patients after hydatidiform mole. Laborious as these assays are, the gravity of chorionepithelioma is such as to justify the trouble. By this means it seems possible that some of the bizarre and irreconcilable results heretofore reported may be avoided.

DR. EMIL NOVAK, BALTIMORE, Md.—The confusion in the nomenclature of the diseases described by Dr. Williams pertains not only to terms but also to interpretations. The intermediate type of lesion, to which the name chorioadenoma destruens was applied by Ewing, is not a clearly defined group. The term itself has always seemed to me a badly selected one, being based on a supposed similarity of the chorionic villi with gland structures, when as a matter of fact they much more strongly suggest, histologically and functionally, the villi of the intestine.

There is rarely any difficulty in the histologic diagnosis of a frankly benign mole or of a frank chorionepithelioma. But there is an intermediate group of cases in which pathologists will differ, chiefly because of differences in criteria as to histologic malignancy. Such attributes as penetration of blood vessels, to which some attach great importance, would seem unreliable in view of the fact that the villi and trophoblast of normal pregnancy penetrate vascular channels, while similar penetration is often seen in hydatidiform moles which by their clinical course are, obviously benign. Nor is trophoblastic overgrowth in itself a safe criterion, as clinically benign moles may show extensive trophoblastic proliferation. This is especially true of villi still attached to the uterine wall, while the degenerated villi usually constituting the grapelike masses filling the uterine cavity may show little or no proliferation.

In the chorionepithelioma on which all pathologists will agree, there is not only a lawless overgrowth of the trophoblast in columns or islands which invade and destroy the musculature, as indicated by extensive coagulation necrosis, but there is usually a loss of the villous pattern. There are exceptions to this, but when this villous pattern is well preserved, I have been inclined to lean backward in the diagnosis of malignancy.

It would seem that the sensible plan is to recognize gradations of malignancy with these lesions as with other forms of malignancy. If the so-called chorioadenoma destruens, or the "malignant mole" of other writers, is really clinically malignant, why not consider it a chorionepithelioma of a lesser degree of malignancy than the very frank chorionepithelioma which I have just discussed? By the same token the term adenoma malignum, used by so many pathologists, is better spoken of as adenocarcinoma of Grade I.

As for the biologic tests, valuable as they are, they may lead us astray, as Dr. Williams has emphasized, so that we are now evaluating them more circumspectly than we formerly did. If the quantitative test remains strongly positive for many weeks or months after the evacuation of a mole, most gynecologists will feel justified in performing hysterectomy, and their attitude cannot be criticized in view of the grave possibilities to the patient. But I am convinced that in a very large propor-

The general incidence of sarcoma of the uterus is doubtlessly somewhat lower than the average of figures quoted in reports of individual observers. This viewpoint seems verified by statistics made available by Dr. Louis C. Kress,³ Director of the Division of Cancer Control of the Department of Health of the State of New York. During the year 1941, as successful operation of the cancer reporting law became a reality in New York State, a total of 1,661 malignancies of the uterus were reported. Thirty-four cases, 2.04 per cent, were reported to be sarcomas, an incidence of one sarcoma for each 48.8 carcinomas of the uterus.

Variation in the reported frequency of sarcoma of the uterus may in part be accounted for by differences in the criteria upon which observers have based their diagnosis. Our own material included 7 cases that should not be considered in a study of sarcoma of the uterus (Table I).

TABLE I. INCIDENCE OF SARCOMA OF THE UTERUS

In the Buffalo General Hospital
1920-1941 Inclusive

DIAGNOSIS OF TUMOR	NUMBER OF CASES	
Fibromyoma of uterus		3686
Carcinoma of the uterus (cervix and fundus)	577	
"Sarcoma of the uterus"	46	
Cases reclassified and omitted		
Uterine sarcoma proved secondary at autopsy	1	
Carcinosarcomas	3	
Atypical myomas reclassified nonmalignant	3	
Total	7	
Sarcomas associated with myomas	12	
Sarcomas in uteri showing no fibroids	27	
Total cases considered as sarcomas	39	
Incidence of sarcoma		
As a malignant tumor of uterus (1 to 15.6 carcinomas)	6.33%	
In patients operated for myomas (1 to 96 fibroids)		1.04%
Associated with degenerating myomas	1 per 307 fibroids	

In one instance at autopsy a previously recorded sarcoma of the uterus was proved to be secondary to primary sarcoma of the adrenal gland. In 3 cases the clinician had recorded a diagnosis of sarcoma on patients in whom the pathologist had noted only atypical cellularity in fibroids. Three other cases of so-called carcinosarcoma had been listed as sarcomas of the uterus. Excluding these 7 cases, the remaining 39 represent an incidence of one sarcoma in every 15.6 malignancies of the uterus, and one sarcoma in each 96 fibroids treated during the years 1920 to 1941.

Malignant Degeneration in Fibroids

Varied interpretation of controversial slides accounts for a wide discrepancy in the reported incidence of sarcomatous change in myomas. Figures as high as 10 per cent have been reported but there is general agreement that not more than 1 per cent of myomas undergo malignant change. Novak and Anderson⁴ reported that 0.56 per cent of their fibroids should be so classified, a figure supported by Kimbrough,⁵ who noted an incidence of 0.76 per cent in his material. Reviewing the histologic reports of 1,400 of our fibroids, in 12 we noted atypical changes that might be interpreted as early sarcomatous transformation. This

SARCOMA OF THE UTERUS*

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TRUE primary sarcomas of the uterus are recognized clinically as highly malignant tumors. Unfortunately the histologic diagnosis of sarcoma in the uterus is often difficult when the neoplastic picture appears in association with myomas. Patient and doctor alike are fortunate in that sarcomas associated with grossly appreciable fibroids often do not prove clinically malignant. So-called secondary sarcomas, these relatively benign tumors, apparently arise by sarcomatous transformation in degenerating myomas.

Our observations regarding sarcoma of the uterus have been largely directed to the problem of diagnosis in the doubtful or borderline case. The records of our patients have been studied in an effort to recognize when cellular irregularities in rapidly growing or degenerating myomas become sarcomas capable of initiating a clinically malignant course. In 57 instances we know the patient's length of survival, date of death, or present physical condition. However, few autopsies have been obtained and in most instances we lack proof that patients died of sarcoma. For the most part, conclusions have been based on the number of patients known to be living at the present time.

Incidence

The records of the Buffalo General Hospital during the past 21 years list the diagnosis of sarcoma of the uterus in 46 cases. Comparing these 46 sarcomas with 3,686 fibroids and 577 carcinomas of the uterus treated during this interval, we found an incidence of one sarcoma in 80 fibroids and one sarcoma in every 12.5 malignancies of the uterus. These figures indicate a surprisingly high incidence of sarcoma compared with Seagriff's¹ report of 3,203 fibroids and 576 carcinomas of the uterus with only 12 sarcomas during the same period of time. However, Goldberger² noted one sarcoma in 100 fibroids, and Smith,³ in 1941, reporting from Memorial Hospital, where a high incidence of malignant tumors would be expected, found one sarcoma in each 47 fibroids examined. Novak and Anderson⁴ have reported that 3.1 per cent of the uterine malignancies sectioned in their laboratory were sarcomas. At the University of Pennsylvania, Kimbrough⁵ found an incidence of 3.2 per cent. Seagriff's report agrees with the frequently quoted figure of one sarcoma to every 40 carcinomas of the uterus. This same frequency was noted by Scudder and Fein⁶ in 1934; by Handley and Howkins⁷ in 1937, and Kotz and Kaufman⁸ in 1938.

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While follow-up data were obtained on 2 of the 3 omitted cases, slides are no longer available and the histologic diagnosis was recorded simply as sarcoma of the uterus. Seven of the 12 tumors arising in uteri containing myomas were considered by the pathologist as originating by sarcomatous degeneration in fibroids. Two of these patients have been followed for over three years, the remaining 5 for over five years, but none of this group have shown any evidence of metastasis or the recurrence of a pelvic tumor. Compared with the rapidly fatal course noted in patients with a giant, mixed or round cell type of tumor, this table shows an occasional long time survival by patients whose tumors were designated as spindle cell sarcoma. Likewise, in the group considered to be primarily of endometrial origin, 3 patients have survived for two and one-half, five, and fourteen years.

One patient surviving fourteen years is of particular interest. Grossly and histologically a typical case of sarcoma botyroides, an 8-year-old girl was treated by Dr. James E. King in 1928, by local excision of the tumor from the cervix followed by two small-dose applications of radium in the cervical canal. Now 22 years old, the patient is having fairly regular periods and on examination the uterus and adnexa appear to be normal. We have noted no other reports in the literature of long term survival of a patient treated for this usually highly malignant form of sarcoma.

Considering the 39 cases listed in Table I, we found that 29, operated prior to 1938, could be utilized in calculating a five-year survival rate. Follow-up information was obtained on all 29 patients in this group. Nine were found to be free of symptoms after five years, a cure rate of 31 per cent. Six of 8 patients operated prior to 1938, in which a sarcoma was found associated with fibroids, have survived over five years. This figure for curability is in striking contrast to the results noted when patients were found to have sarcomas unassociated with myomas of the uterus. In this group only 3 of 21 patients survived five years, a five-year survival rate of 14.3 per cent in primary uterine sarcomas.

Symptomatology

The diagnosis of sarcoma of the uterus is rarely made before operation. The symptoms and findings usually suggest a preoperative diagnosis of fibromyoma of the uterus. Observers agree that irregular vaginal bleeding is the most frequent complaint. Watery discharge is often noted by patients with an endometrial type of sarcoma. A rate of growth more rapid than ordinarily noted in benign tumors should warrant a suspicion of the malignant character of the neoplasm. The case recently reported by Anderson and Lomax¹¹ emphasizes the malignant potentialities of rapidly recurring polyps. Abnormally rapid growth should always be regarded with suspicion in spite of a reassuringly negative histology. Pain has been frequently noted as a comparatively early symptom in sarcoma as compared to the late occurrence

represents one fibroid showing areas of atypical cellularity in each 116 myomas examined, an incidence of 0.85 per cent. It is interesting to consider this figure in view of the fact that among sarcomas found in our Hospital, while 12 were associated with myomas, only 7 were considered examples of sarcomatous transformation in degenerating myomas. Our incidence of malignant degeneration in fibroids is therefore only 0.19 per cent, one sarcoma in each 526 fibroids.

Classification

Classifications of sarcomas of the uterus generally prove unsatisfactory because, as Novak¹⁰ has concisely stated, "the invasive tendency of sarcoma soon tends to blot out the evidences of its origin." In relatively early cases grouping can be based on the suspected tissue of origin, but in the majority of reports sarcomas of the uterus have been classified according to the dominant type of neoplastic cell (Table II). Grouping

TABLE II. PROGNOSIS IN SARCOMA OF THE UTERUS
Classified According to Histology of Tumor

HISTOLOGIC GROUPING	TOTAL CASES	CASES LIVING	LENGTH OF TIME SURVIVORS FOLLOWED	DECEASED	LENGTH OF SURVIVAL
Sarcomatous degeneration in fibroids	7	7	2-3 years 4-5 years 1-6 years	0	—
Giant cell sarcoma	2	0	—	2	1-2 mo. 1-10 mo.
Mixed cell sarcoma	3	0	—	3	1-op. 1-2 mo. 1-6 mo.
Round cell sarcoma	4	0	—	4	2-2 mo. 1-6 mo. 1-36 mo.
Spindle cell sarcoma	10	2	1-12 years 1-14 years	8	1-7 1-op. 1-1 mo. 1-2 mo. 3-6 mo. 1-16 mo.
Endometrial sarcoma	10	3	1-2½ years 1-5 years 1-14 years	7	2-2 mo. 1-3 mo. 1-9 mo. 2-12 mo. 1-22 mo.
Totals	36	12	—	24	—

Of 29 cases operated prior to 1938, 9 (31%) have survived 5 or more years.

Of 8 sarcomas associated with fibroids operated prior to 1938, 6 (75%) have survived 5+ years.

Of 21 sarcomas in uteri not containing fibroids operated prior to 1938, only 3 (14.3%) have survived 5+ years.

our cases in this manner, when the cell type is correlated with the patient's clinical course, there is noticeable variation in the degree of clinical malignancy manifest by different types of sarcoma. Three of the 39 sarcomas listed in Table I have been excluded from this grouping.

Discussion

• Credit for the first attempt to correlate the histologic picture with the patient's clinical course should go to Proper and Simpson,¹⁵ who in 1919 noted large atypical nuclei and giant cells occurring in direct proportion to the clinical degree of malignancy. In doubtful cases these observers suggested the absence of mitotic figures as a dependable criterion of benign growth. Their interpretation of the significance of mitotic figures has been repeatedly verified by later studies. Difficulties in interpretation of the histology of these uterine sarcomas were evident in 1920, when Evans,¹⁶ quoted Kelly and Cullen as stating that while they found 17 sarcomas of the uterus among 1,400 myomas removed, during the same period of time they had noted 17 other tumors in which the diagnosis of sarcoma was questionable. Combining a correlation of the histology and the clinical course of the patient, Evans reported an evaluation of 9 histologic characteristics previously described by various observers as reliable criteria of the sarcomatous picture. His method involved highly technical and painstaking work in order to make the actual count of mitotic figures upon which he based an estimate of the prognosis. Significantly he noted no gradual gradation in the number of mitotic figures and emphasized that sections of the tumors examined contained either (1) very many, (2) few, or (3) practically no mitotic figures. This finding has suggested to many observers that even a rough estimate of the frequency of mitotic figures would provide a practical means of judging the prognosis in an individual case.

In addition to evaluating the presence and number of mitotic figures, Evans described the appearance and significance of giant or atypical nuclei in myomas. He accepted Wilson's¹⁷ observation that atypical or giant nuclear forms were evidences of amitotic division among degenerating cells. According to Evans, Wilson had shown that a division of the nuclear material might occur without a corresponding division of the cytoplasm. This process Wilson had interpreted as direct cell division, and he regarded it as an indication of degeneration in the cells involved. In discussing the significance of atypical or giant nuclei in fibroids Evans noted that bizarre nuclear forms had been reported in cultures of irradiated tissue in which similarly atypical nuclei appeared as degeneration replaced active proliferation.

Schmitz,¹⁸ in 1941, described the prognostic significance of atypical and bizarre nuclear forms observed in repeated biopsies taken from cervical malignancy during the course of roentgen therapy. In Schmitz's material it was apparent that atypical or giant nuclei forecasting clinical arrest of the malignancy should be regarded as evidence not of proliferation, but of the degeneration of tumor cells. This interpretation of the significance of so-called giant or atypical nuclei seems equally applicable to similar atypical cells in degenerating myomas. At least in our material we have noted no evidence that such cellular irregularities

of pain in carcinoma of the uterus. To make the diagnosis when malignancy of the uterus is removable we must remain apprehensive concerning irregular or post-menopausal bleeding. Hopeless malignancy will develop if we readily conclude that abnormal bleeding is due to a palpable, but possible incidental fibroid.

Treatment

Effective treatment of sarcoma of the uterus depends upon wide surgical removal of all pelvic tissue that can be sacrificed. The predisposition of these tumors to postoperative thrombo-embolism should be remembered. Care should be taken to avoid injuring venous channels proximal to the point of ligation. After a subtotal hysterectomy for supposedly benign fibroids, when sarcoma is reported, the operator is confronted with the problem of possible malignancy in the remaining cervix. Dannreuther¹² and others have expressed the opinion that a secondary operation for removal of the cervix subjects the patient to greater danger than the probability of extension from the cervix. A study of our material substantiates the wisdom of a conservative course, although in at least one instance we could ascribe recurrence of pelvic sarcoma to extension from a cervical stump. In a majority of cases it seems probable that sarcoma arising in the fundus and involving the cervix at the time of operation would have extended beyond removable limits, in which case secondary removal of the retained cervical stump could add nothing to the five-year salvage among these patients. Several observers have reminded us that radium can be satisfactorily applied postoperatively in the cervical stump, a measure involving far less risk to the patient than a secondary operation for removal of the cervix.

According to Masson,¹³ the 1920 German Gynecological Council concluded that results following irradiation therapy were so good that no operation was advised when this diagnosis was proved or suspected. In his own material Masson noted that irradiation was of no appreciable value in at least one-fourth of the cases treated at the Mayo Clinic. Our observations suggest that palliative benefit can be realized by irradiation of the more anaplastic types of uterine sarcoma. The relatively long survival of several patients in Groups C and D treated by radium and x-ray therapy is shown in Table III. The effectiveness of irradiation is most apparent in patients treated preoperatively by intrauterine applications of radium for suspected carcinoma of the uterus. Healy¹⁴ and others have expressed pessimism regarding the results of irradiation in sarcoma of the uterus. However, on the basis of comparatively limited observations, we believe it would be advisable to employ intrauterine radium before panhysterectomy in the treatment of the highly cellular sarcomas of endometrial origin. On the other hand, we have found that postoperative roentgen therapy appears to accomplish very little, particularly in cases of the histologically more mature types of myogenic sarcoma.

TABLE III. PROGNOSIS IN ATYPICAL MYOMAS AND SARCOMA OF THE UTERUS

Study of 60 Cases: 45 Sarcomas of the Uterus, 15 Atypical Myomas
Classified According to Suggested Grouping

GROUPS	TOTAL CASES	CASES LIVING	LENGTH OF TIME SURVIVORS FOLLOWED	DECEASED	LENGTH OF SURVIVAL
A Degenerating or soft rapidly growing myomas, atypical nuclei, or few mitotic figures	15	14	0—under 18 mo. 5—1½ to 3 yr. 5—3 to 5 yr. 4—over 5 yr.	1	2½ yr.
B Sarcomas associated with fibromyomas, atypical nuclei, and noticeable mitotic figures	14	10	1—under 18 mo. 0—1½ to 3 yr. 3—3 to 5 yr. 6—over 5 yr.	4	1—? 1—6 mo. 1—9 mo. 1—17 mo.
C Sarcomas in uteri not containing fibroids	28	4	0—under 18 mo. 1—2 yr. 1—12 yr. 2—14 yr. R	24	2—operative 11—1 to 3 mo. 4—3 to 6 mo. 4—6 to 12 mo.** 1—22 mo. 1—36 mo.* 1—?
D Carcinosarcomas, highly anaplastic undifferentiated cells (not two neoplasms combined)	3	0	—	3	1—? R 1—2 yr. R 1—2½ yr. R
Totals	60	28	—	32	—

Cases treated by radium without hysterectomy (R) or prior to hysterectomy (*) are indicated.

**Two of 4 cases, surviving six to twelve months, and *one case surviving thirty-six months, treated by radium before hysterectomy.

Group A includes rapidly growing soft myomas containing a noticeable number of mitotic figures, but with preservation of a fairly regular arrangement in spite of increased cellularity. In this group we would also place fibroids in which sections show atypical polymorphic or giant nuclear forms, usually in or adjacent to areas of degeneration in myomas. Fifteen patients in this group have been followed, 9 for over three years and 4 for over five years with no evidence to suggest that a clinically malignant tumor was overlooked at the time of operation.

Group B includes cases in which histologic section of a grossly appreciable fibroid reveals atypical nuclear forms *and* mitotic figures, evidences of the active proliferation of atypical cells. Twelve of these patients were noted in Table I as sarcomas associated with fibroids. Two additional cases, discovered in reviewing the histology of 1,400 fibroids, had not been properly filed in the record room and are included here as the thirteenth and fourteenth secondary sarcomas followed. Obviously Group B includes secondary sarcomas in myomas as well as primary sarcomas (belonging in Group C). We believe the majority of the clinically malignant tumors in this group are primary sarcomas associated with an incidental fibroid. For a practical estimate of the prognosis, if there was a grossly appreciable fibroid, we have placed the tumor in Group B.

in myomas indicate a potentially malignant tumor. However, it must be emphasized that when similarly atypical cells appear in a tumor containing a noticeable number of mitotic figures a clinically malignant tumor should be suspected and a guarded prognosis given.

Our interest in sarcoma of the uterus was originally stimulated by observation of 2 patients whose malignant course was not predicted by the histology of the tumor removed. It seemed possible that other patients with equally malignant tumors might have been overlooked and their eventually malignant course not reported to us. With that possibility in mind we reviewed the histologic reports of 1,400 consecutive fibroids. Atypical cellularity was noted in 12 myomas, an incidence of 0.85 per cent, or one fibroid that might be viewed with suspicion in each 116 removed. Follow-up data on these 12 patients reveal that 11 have survived periods varying from eighteen months to over five years. Five have noted no signs of recurrent pelvic tumor during an interval of three to five years, while 4 have been perfectly well over five years. One of the 12 died two and one-half years after operation but no autopsy was held, and we could obtain no reliable information concerning the recurrence or absence of a pelvic tumor.

The records of the 12 patients showing atypical cellularity in fibroids have been added to the data of 3 similar cases reclassified nonmalignant in Table I. This combination provided us with a total of 15 patients to be regarded as borderline or potentially malignant fibroids. Obviously these 15 tumors were histologically atypical myomas and are not to be considered as sarcomas of the uterus. However, we have observed two patients develop a rapidly recurrent and clinically malignant tumor of the pelvis soon after removal of histologically benign but atypical myomas. In such instances routine histologic sections may have failed to portray a malignant picture that would have been apparent had more sections of the tumor being studied. Careful reexamination and additional sections would undoubtedly insure closer correlation of the histology and the clinical course. On the other hand, one purpose of this study has been to determine the reliability of routine histology in these doubtful or borderline cases. Tumors have been classified entirely on the basis of the pathologist's routine reports. On the basis of the follow-up data to be reported in Table III, we conclude that fibroids showing areas of atypical cellularity should not be viewed with alarm unless the histology warrants a diagnosis of established sarcoma.

Proposed Classification

Considering the data in Table II we were impressed by the relatively long survival of patients whose sarcoma was associated with a grossly appreciable fibroid. Seeking a practical basis for an estimate of the prognosis in an individual case, we have reclassified 60 patients into 4 groups as indicated in Table III.

- D. Certain highly anaplastic tumors of the uterus are frequently classified as carcinosarcoma. In a majority of these cases the histologic picture indicates a highly malignant tumor difficult to classify rather than the presence of coexisting carcinoma and sarcoma.

Patients in this group provide the more radiosensitive of the tumors classified as sarcomas of the uterus, but early extension or local recurrence is the rule. Death due to metastasis may occur in spite of apparent local eradication of the tumor.

Conclusions

Fibroids showing areas of atypical cellularity should not be viewed with alarm unless the histologic changes justify a diagnosis of established sarcoma.

The prognosis of patients with sarcoma of the uterus primarily depends upon the state of the disease when adequate treatment is instituted. To a lesser degree prognosis varies with the histology of the tumor.

A comparatively simple basis for the classification of sarcomas of the uterus is suggested as an aid in estimating the degree of clinical malignancy.

A general attitude of pessimism is not justified in the management of patients with sarcoma of the uterus. Among the patients followed in this study and in a majority of similar reports in the literature, the percentage of five-year survivals is approximately 30 per cent.

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Discussion

DR. WILLIAM H. VOGT, St. Louis, Mo.—When Dr. Randall sent me his paper for review only a few days ago, I was immediately impressed with the large number of sarcomas of the uterus reported. His figures show that even when all sarcomas

Group C consists of tumors frankly sarcomatous arising in uteri not containing fibroids. It is evident that a majority of patients with a true primary sarcoma of the uterus consistently run a rapidly fatal course.

Group D comprises the small group of highly anaplastic tumors usually designated as carcinosarcoma. The literature regarding this particular group of tumors provides a comprehensive discussion of the various histologic pictures frequently classified as carcinosarcomas. Hoffman¹⁹ has called attention to the rarity in which this picture is due to co-existing carcinoma and sarcoma in the same uterus. Handley and Howkins⁷ emphasize the difficulties of accurate diagnosis in this group of cases. They advise consideration of the possible effects of (a) secondary infection, (b) previous irradiation therapy, or (c) sarcomatous infiltration of a secondarily invaded and distorted epithelial surface. At least two of the three cases in our series were in all probability highly malignant anaplastic carcinomas. They are included here because we wish to mention later the comparative radiosensitivity of these tumors compared to other types of uterine sarcoma.

We believe this proposed grouping provides a practical basis by which sarcomas of the uterus may be classified. Our observations suggest this grouping may prove an aid in estimating prognosis in the individual case. The relationship between prognosis and the proposed grouping is indicated in the following outline:

- A. The presence of a noticeable number of mitotic figures in rapidly growing myomas or the finding of giant cells—atypical polymorphic nuclear forms, in or adjacent to degenerating areas in leiomyomas, may be regarded as criteria warranting a suspicion of sarcomatous change, but neither finding alone should imply a clinically guarded prognosis.

Patients in this group should not be considered as harboring a malignant tumor and so-called prophylactic irradiation therapy is not justified.

- B. Histologic evidence of actively proliferating atypical cells in patients with a grossly appreciable myoma—the presence of mitotic figures and atypical nuclear forms, warrants a diagnosis of sarcoma, arising either as a result of so-called sarcomatous degeneration in a fibroid or as a primary sarcoma associated with an incidental myoma.

Patients in this group should be treated by radical surgery. A guarded prognosis should be given as recurrence or extension of a clinically malignant tumor may be expected in a definite proportion of these cases.

- C. Histologic diagnosis of sarcoma in a uterus not containing fibroids usually foretells a rapidly fatal course irrespective of the type of predominating cell or the apparent histogenesis of the tumor. In a striking percentage of cases operative removal of this type of tumor is followed by death from vascular accidents during hospital convalescence. Preoperative irradiation may decrease the number of postoperative deaths due to thromboembolism but the majority of primary sarcomas of the uterus are relatively resistant to irradiation therapy and usually only palliation can be expected.

pattern, the polypoid masses being bulky, infiltrative, and friable. The same thing is true of growths arising in the endocervix, so that if one removes a polyp which, instead of the fragile structure of most cervical polyps, is of this bulky friable structure, one should suspect sarcoma.

Diagnosis is ordinarily not made until, or even more frequently, after operation. Curettage may at times reveal the lesion preoperatively, but more often not. The microscopic diagnosis is often easy enough, but, as with other types of malignancy, there are borderline cases concerning which pathologists differ. In most of these cases this doubt is of very little practical disadvantage, as they are likely to be of a low degree of malignancy.

If the microscopic section shows the muscle cells uniform in size and nuclei, making due allowance for the differing angles of section of the muscle bundles, there is no justification for the diagnosis of sarcoma, no matter how cellular the growth. The criteria of malignancy here, as with sarcoma in general, are disparity in the size of the cells, and of the nuclei, with mitosis, hyperchromatosis, and other evidences of anaplastic activity. Giant cells are perhaps most often of the symplasmic variety, due to blending of the cytoplasm of adjoining cells in degenerating areas of the tumor. I agree with Dr. Vogt that in Dr. Randall's suggested classification, there is no reason for the separation of Groups A and B, both of which pertain to sarcoma originating in myoma, though the degree of malignancy may of course differ very widely.

DR. JAMES E. KING, BUFFALO, N. Y.—My interest in this subject arises from the fact that two of my patients form a part of Dr. Randall's report. One was the girl of 8 years who had a sarcoma butyroides. I told the parents that the outlook was very unfavorable, but the patient comes in to see me occasionally, still in very good health, now 19 years of age and is having normal menstrual periods. She has a perfectly normal pelvis.

The other case was a patient from whom I removed polyps every two or three months over a period of about a year and a half. These polyps were always reported by the pathologist as benign. Clinically these recurrent polyps were not benign and I felt that there was very definitely more than a suspicion of sarcoma. Later the uterus was removed and found to contain several additional polyps and several tumors that appeared to be fibromas. That was less than a year ago and the woman now has a large recurrence that occupies the entire pelvis and much of the abdomen.

The classification was primarily an attempt to find a distinction between Groups "A" and "B," and next to call attention to the purely clinical observation that sarcoma in association with fibroids is usually not a rapidly fatal tumor. On the other hand, the diagnosis of sarcoma when there is no fibroid confusing the histologic picture foretells a rapidly fatal course. The tumor may prove radiosensitive, and simply because sarcoma is included in the nomenclature of a neoplasm does not mean that irradiation may not be of benefit.

DR. RANDALL (closing).—I am afraid that I failed to make clear the distinction between Groups "A" and "B." Two pictures of atypical cellularity may be seen associated with myomas. In the first there are very atypical, giant or bizarre nuclear forms. Such atypical nuclei, usually noted in degenerating myomas, are not an indication of malignancy. Secondly, there may be impressive numbers of mitotic figures in rapidly growing myomas, but alone, mitotic figures are not an indication of malignancy. On the other hand, when sections of the uterus show strikingly atypical cells plus mitotic figures, such a combination spells sarcoma. In Group A there are atypical nuclei or mitotic figures, in Group B both atypical nuclei and mitotic figures. That was the distinction between tumors placed in Groups "A" or "B."

of the uterus associated with fibroids are eliminated, 4.7 per cent of all malignancies of the uterus are sarcomas. Since the essayist's percentage seemed rather high, I investigated the records at our own hospital. Here I found that out of the last 391 cases of malignancy of the uterus there were 11 cases of sarcoma. Ten of these were sarcoma of the uterus proper, one of the endometrium, and there was no sarcoma of the cervix. Two of the sarcomas of the uterus were associated with fibroids. If we eliminate these two cases, as the author has done in his series, we then have a figure of 2.3 per cent. Unfortunately, time did not permit an investigation of the outcome of our recorded cases.

Classifications of sarcoma of the uterus vary greatly and are confusing. Dr. Randall attempts to establish criteria on which to base an estimate of the prognosis. I can, however, see little difference in his Group "A" and Group "B" cases. Included in both of these groups are tumors in which atypical polymorphic or giant nuclear forms appear in fibroids. In both groups mitotic figures are present. I am sure that no one would claim that the presence of mitotic figures was necessarily evidence of malignancy. A fibroid, for instance, having the appearance of a normal tumor except for a few more cells than usual and containing one or two mitotic figures to every 10 or 20 high power fields, should not be considered as a sarcoma but simply as a rapidly growing non-malignant tumor. If, however, the tumor is very cellular it might be looked upon as suspicious.

Considerable interest has lately been aroused by the degree of nuclear activity as indicated by the mitotic count. Evans and Kimbrough found, for instance, that the mitotic count parallels, as a rule, the degree of clinical malignancy. Novak relates his experience with the mitotic count and states that of 20 cases in which 0 to 5 mitoses were found in 20 fields, 15 were living more than 3 years after operation, 1 received only palliative treatment and presumably died, and 3 were not traceable. On the other hand in 7 patients with mitotic counts above 30 and up to 88, all are known to have died. He said: "It would therefore seem that when the mitotic count is low, recovery is the rule."

No one, I think, would argue with the essayist about his "C" and "D" groups. These are highly malignant tumors running a rapidly fatal course.

To attempt a classification as Dr. Randall has outlined is undoubtedly desirable, but I am wondering whether by this means we will be in any better position to grade the degree of malignancy of a given tumor. The old classification of spindle cell, round cell, and mixed cell and, perhaps, giant cell tumor is probably as satisfactory as any, remembering that the unripe or undifferentiated cells are the most malignant and the spindle cell type of the leiomyosarcoma with considerable differentiation is of the lowest grade of malignancy. This, coupled with an accurate mitotic count, will, in the majority of instances, answer our needs.

DR. EMIL NOVAK, BALTIMORE, Md.—Several years ago we reported from our laboratory a series of 59 cases of sarcoma of the uterus, with statistical results quite comparable to those reported by Dr. Randall. The gross appearance of a myoma will often justify the presumption of its benign or malignant nature. If the tumors are opened in the operating room, as they should be, and the cut surface is hard, glistening and whorl-like, one need have little fear of sarcoma. If, on the other hand, the cut surface shows a soft, pultaceous area, with often a ragged central cavity, one should at least suspect the existence of sarcoma. The common hyaline degeneration is more likely to present areas of amorphous, jelly-like appearance, with a tendency to the liquefying changes constituting cystic degeneration.

The mere fact that a sarcomatous uterus is nodular in appearance does not justify the conclusion that the sarcoma originated in myoma, because sarcoma arising in the uterine wall not infrequently grows in a nodular fashion. In other cases the growth is diffuse and more or less symmetrical. When the origin is in the endometrium, as it not infrequently is, it characteristically assumes a polypoid

The attachments of the vaginal tube laterally and posteriorly to the endopelvic fascia covering the levators ani, the cervicopubic fascia anteriorly, the cul-de-sac peritoneum and uterosacral ligaments posteriorly, Mackenrodt's ligaments at each lateral fornix and finally to the vaginal portion of the cervix—all are extremely vulnerable to detachment.

The importance of a normal relationship between the vaginal walls and paravaginal supporting tissues has long been recognized. Mengert concluded following his experiments on cadavers, "that the paravaginal supports are fully as important as the parametrial, if not more so, in uterine support." Damage to the vagina is reported as detachment from specific areas or obliteration of fornices.

Vesical and anal sphincter damage was recorded as incontinence; congenital defects were eliminated. There were 20 in the group of 461 primiparas and 32 in the 539 multiparas who gave a history of incontinence either continuously or on lifting or coughing.

Anal sphincter incontinence was not encountered in 5 patients with third-degree laceration and repair. Much damage no doubt occurs to fascial planes not easily observed or recorded. The anterior compartment of the ischiorectal space which adds support to the pelvic diaphragm most certainly is damaged in each case as is true of the superficial perineal structures.

It must be made clear that the intent of this paper is to record tissue damage due to parturition as interpreted by postnatal examination. Consecutive cases were studied without regard for correction due to age, race, size of baby, bony pelvis, or method of delivery. These factors have been recorded and will be added at a later date in larger groups.

Material

Two main groups, multiparas and primiparas, were divided into three divisions. First, those delivered without apparent laceration. There were 456 multiparas and 209 primiparas in this group. Second, those delivered with laceration and repair, there being 109 primiparas and 61 multiparas. And third, those with episiotomy and repair. There were 143 primiparas and 22 multiparas in this group. Those delivered with laceration and repair were segregated for the obvious reason that some of the damage sustained might have been corrected by the repair.

Review of the damage observed in the entire group reveals parturition as a destructive process. Three hundred and thirteen (31 per cent) of patients suffered damage with resultant atrophy or detachment to the levators ani, varying from partial to complete damage of one or more components, the pubococcygeus being most vulnerable. One hundred and seventy-eight (18 per cent) manifested detachment of the urethra from its normal retropubic position indicating damage to that portion both of pelvic diaphragm and urogenital trigone. Three hundred and eighty-nine (39 per cent) had gaping of introitus when relaxed, and of these, 143 (14 per cent) remained gaping when voluntary effort at closure by levators was observed. Two hundred and thirty-five (24 per

POST-PARTUM OBSERVATION OF PELVIC TISSUE DAMAGE*

HAROLD L. GAINES, M.D., KANSAS CITY, MO.

THESE cases chosen for report represent the last 1,000 patients examined in the postnatal clinic of the obstetric and gynecologic department at the University of Kansas. The primary objective in this study was the teaching of gynecologic anatomy to graduate and undergraduate students. The need for this is readily recognized because of the limited number of female specimens in the anatomy department and, following this, only in the rarest instance is there any further possibility for study. It therefore remains that the clinic and operating rooms are the only places providing this opportunity.

Intelligent management of the obstetric patient with preservation of tissues and reconstruction of damage demands a knowledge of the structures. Simultaneously, observations were recorded and are now presented in the form of a preliminary report.

Three definite anatomic planes are of recognized importance, and damage may be observed in an objective manner. The upper pelvic floor is made up of the parametrial fascia with its localized condensations forming the uterosacral, Maekenrodt's ligaments and the much weaker cervicopubic fascia. Damage to this plane is manifested by cystocele, uterine descensus, and enterocele.

The pelvic diaphragm consists of the pubococcygeus, ileococcygeus and coccygeus muscles with their envelope of endopelvic fascia. Damage to this plane was recorded by palpation of areas of detachment, or atrophy, of the first two, relaxation of the introitus after voluntary effort at closure, and detachment of the urethra from its retropubic position.

According to Curtis and Anson it is the pubococcygeal division of the levators ani that affords continuous support for the organs of the urogenital and pelvic parts of the perineum; the iliococcygeus completes the diaphragm at the sides and behind but does not come in contact with the viscera.

The third plane, the urogenital trigone, closing the anterior triangle of the bony outlet with its fascial planes and musculature inclusions, is one of the areas most vulnerable to damage due to parturition. Damage to this plane was recorded by noting relaxation of the vestibule, detachment of urethra and by comparing with normal the "anovaginal" portion as determined by digital rectal examination. In addition to these planes of tissue structure, other injury occurs which is of vital importance to the patient's welfare.

*Presented, by invitation, at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 10 to 12, 1942.

parison. When the two groups, multiparas and primiparas, are compared, it is apparent that multiparity increases tissue damage in a great degree to all areas except the levators, where it occurs to a lesser degree.

An exposition of the damage in the various groups and areas can best be seen in the illustrations (Figs. 1 to 7) and Tables I and II.

*Multipara Without Laceration
Cases 456*

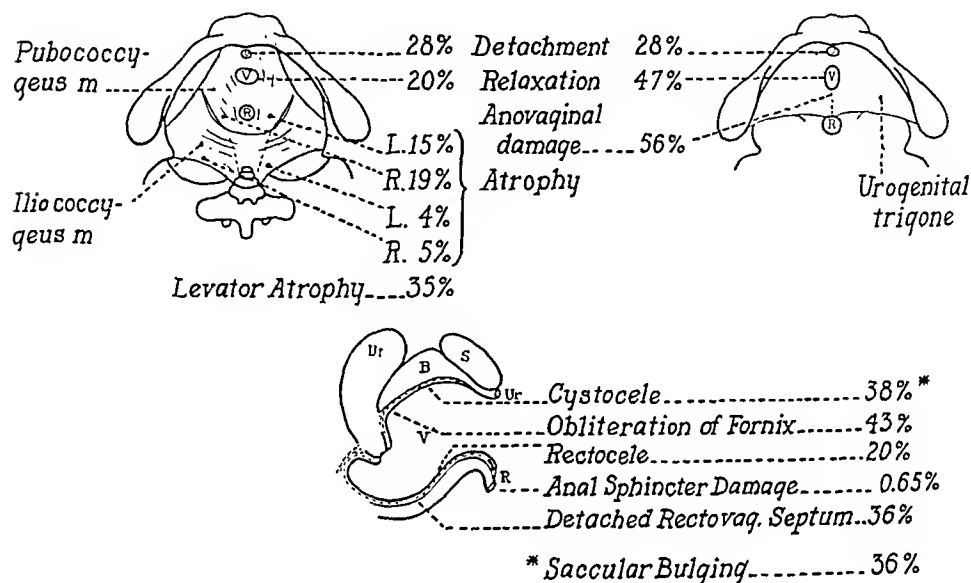


Fig. 2.

*Multipara With Laceration and Repair
Cases 61*

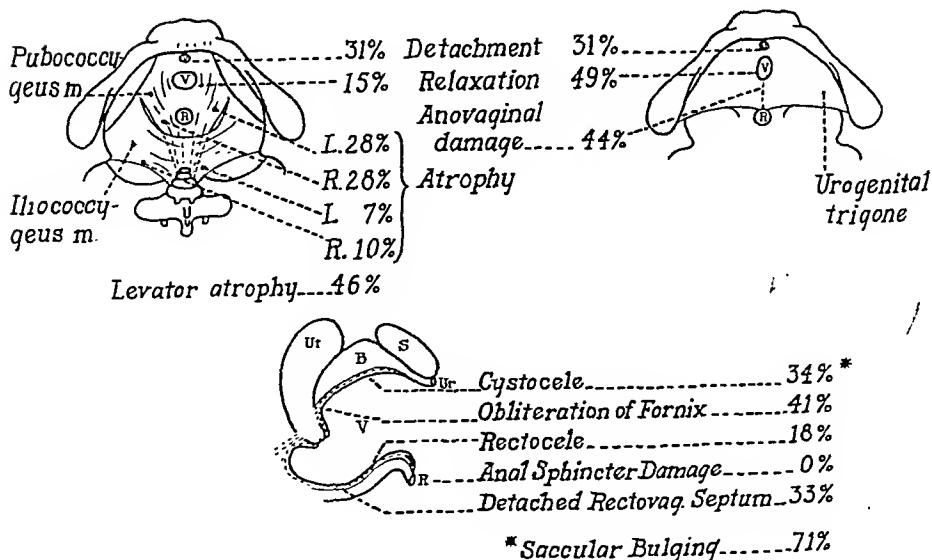


Fig. 3.

cent) showed what was arbitrarily set as less than 60 per cent of normal height or thickness of the anovaginal portion of the urogenital trigone. Only those having less than 60 per cent were chosen because of the difficulty in establishing a normal. For this reason the percentage suffering injury is much less than actually exists, as this is one of the most frequently damaged areas. Episiotomy offers greatest protection to this area as will be seen when the two groups of primiparas with episiotomy and those delivered without apparent laceration are compared.

Difficulty was encountered in accurately recording damage to vaginal wall attachments; yet, its importance is great.

Postpartum Patients

Cases 1000

Primipara without laceration.....	209	Multipara without laceration.....	456
Primipara with laceration and repair..	109	Multipara with laceration and repair....	61
Primipara with episiotomy and repair..	143	Multipara with episiotomy and repair....	22

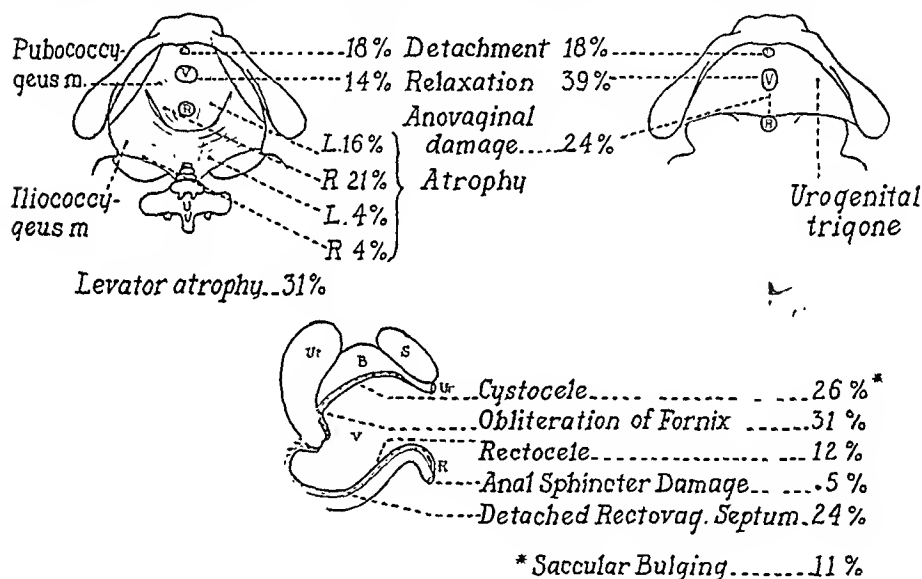


Fig. 1.

Two hundred and thirty-six (24 per cent) of the patients showed detachment of the vaginal wall from the endopelvic fascia on either side of the rectum and actual rectocele recorded in 120, or 12 per cent. Diffuse detachment or prolapse was noted in 202, or 20 per cent. Obliteration of the anterior fornix was partial to complete in 311, or 31 per cent. Cystocele as interpreted by definite saccular or diffuse bulging of anterior vaginal wall was present in 264 patients, saccular bulging being 11 per cent of total. Enterocoele was not observed.

Nine instances of uterine descensus were observed, and in only one was it complete, all being in multiparas.

A comparison without the corrective factors mentioned is not justified but nevertheless it was interesting to note the like percentages of damage in the 3 groups of primiparas, the exception being in the "anovaginal" portion of the urogenital trigone in which case those with episiotomy and repair were benefited. The groups of multiparas are too small for com-

Primipara With Episiotomy and Repair
Cases 143

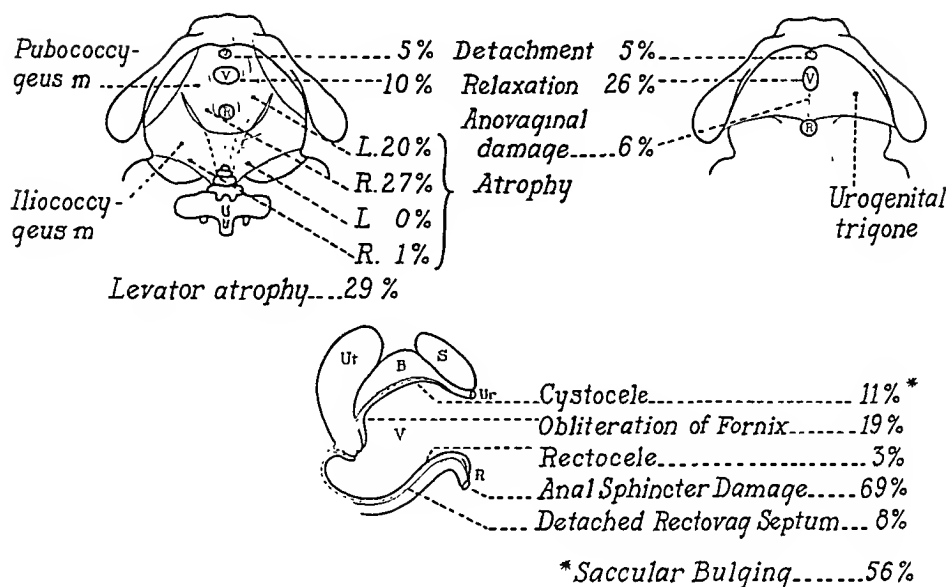


Fig. 6.

Primipara With Laceration and Repair
Cases 109

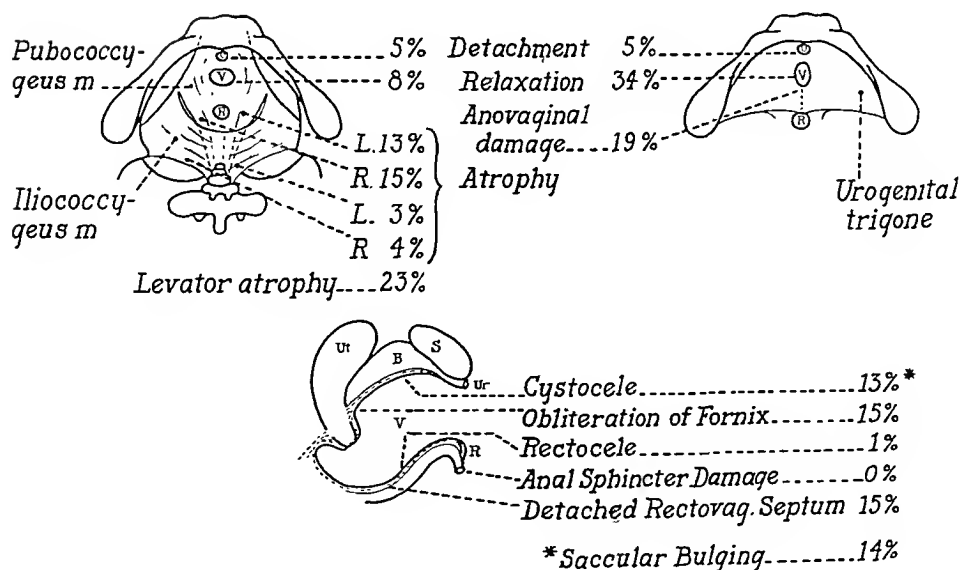


Fig. 7.

Multipara With Episiotomy and Repair
Cases 22

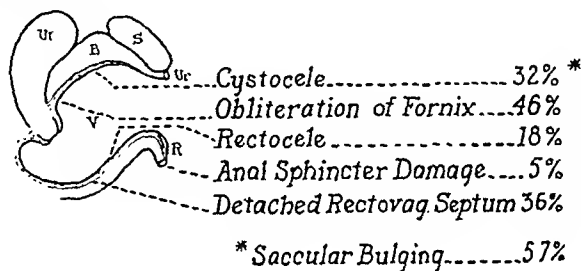
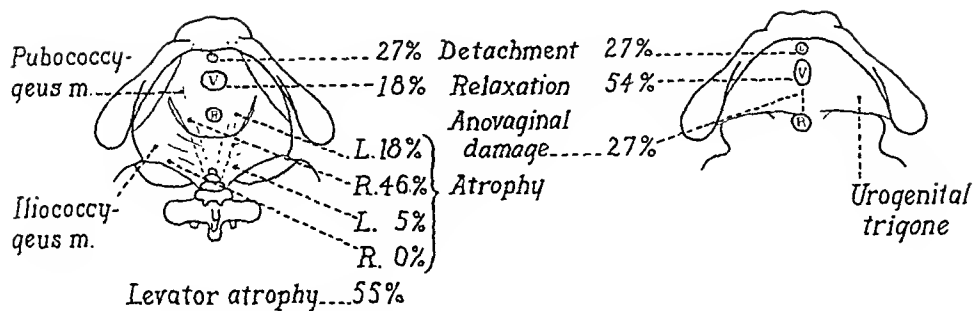


Fig. 4.

Primipara Without Laceration
Cases 209

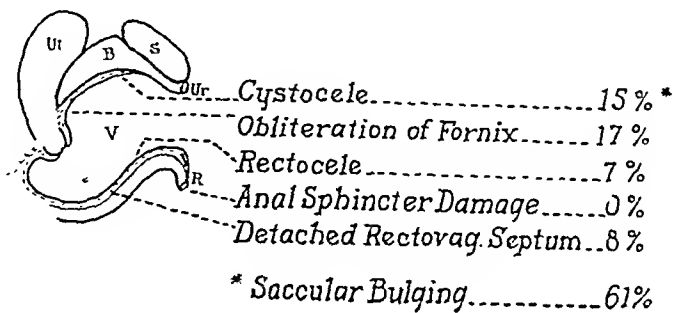
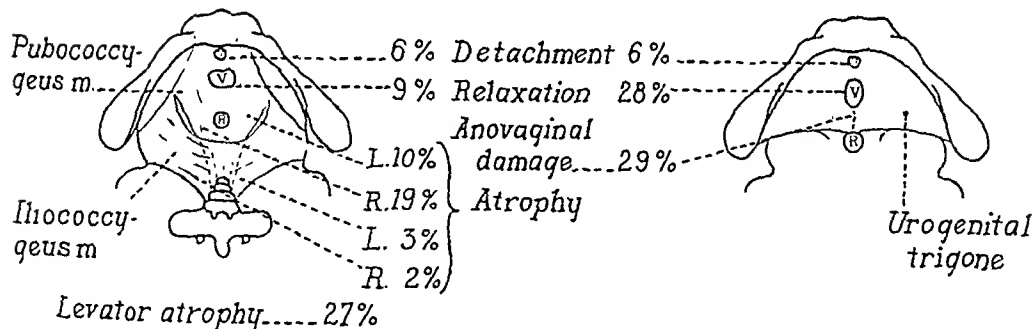


Fig. 5.

I am of the impression that our results, where episiotomy has been employed during the delivery of the primigravida patient, have been somewhat better than those described by Dr. Gainey. In this observation I may be entirely wrong and perhaps more detailed study of our own cases would indicate such. However, with the free use of median episiotomy, extended when necessary off to the side of the anus and the rectum, we have been able to avoid extensive urogenital trigone damage. In fact, I think the main indication for episiotomy is to prevent pressure of the head against the bladder, the urethra, and the fascial structures of the urogenital diaphragm.

To accomplish this with episiotomy, certain principles must be kept in mind: (1) Episiotomy must be performed early and before the head has greatly distended the lower birth canal; (2) episiotomy must be free (we prefer a median incision down to the sphincter and then an extension to the left of the sphincter toward the ischio-rectal fossa); (3) the repair of this incision must be conducted with just as great care as a gynecoplastic operation, which means that the field must be cleared of blood, must be properly exposed, and the procedure done in an orderly anatomic fashion; (4) the use of fine grades of catgut, notably 00 chromic catgut which we formerly used. There is very little tension in this area and all that one needs is material of sufficient tensile strength to hold the tissues together.

Where I find the greatest degree of damage of fascial structures and underlying muscle tissue is in the slender primipara who has a rapid, almost precipitous labor. Here, as Dr. Gainey has pointed out, damage of the urogenital diaphragm occurs, submucous injuries of the pubococcygeal portion of the levator ani muscle, rupture of the true ligaments of the uterus and a resulting early tendency to cystocele, rectocele, and descent of the puerperal uterus. While the slow, difficult labor of the less feminine type of patient may be more worrisome to the obstetrician, generally there is better recovery from tissue damage.

Finally, from the study of Dr. Gainey's paper, I am convinced that there is more to the examination of the postnatal patient than I have been practicing and I shall go back to this phase of our obstetric work with a renewed interest; thanks to this stimulating presentation.

DR. L. A. CALKINS, KANSAS CITY, KAN.—Assumption of damage in some of these areas, particularly in the anovaginal region, may easily be a matter of personal opinion. In order that his data be as accurate as possible Dr. Gainey did 500 of these patients and then discarded this group before reporting 1,000 cases examined since that time. I think there can be little question as to the accuracy of the damage reported in this study.

None of us has learned how to examine the pelvis completely and this presentation is perhaps a beginning in that direction. When we have learned to do this we will perhaps be in a position to determine whether a woman should have an episiotomy or not.

DR. A. J. RONGY, NEW YORK, N. Y.—I agree with Dr. Calkins that most of us do not know how to examine the pelvis and that we do not understand its anatomic construction. E. K. Roberts has probably made the most extensive study of the soft structures of the pelvic floor. He concluded that the uterus is held in position at a fixed point in the pelvis, slightly above the internal os, by a diaphragm composed of connective and muscular tissue and their blood vessels. It is these structures, or the upper diaphragm, as he terms it, which when injured during labor cause the uterus to be dislocated from the fixed position.

The mechanism which injures the lower structures of the soft pelvis largely depends upon the construction of the bony outlet of the pelvis. If an imaginary line is drawn across the ischial tuberosities, the pelvic outlet is divided into an anterior

TABLE I. COMPARISON OF DAMAGE

	MULTIPARAS 539	PRIMIPARAS 461
Rectocele	19%	3%
Rectovaginal septum detachment	35%	9%
Prolapse vaginal walls	28%	10%
Obliteration anterior fornix	43%	17%
Cystocele { Saccular	38% { 15%	13% { 6%
{ Diffuse		
Urethral detachment	28%	5%
Anovaginal trigone damage	53%	20%

TABLE II. COMPARISON OF LEVATOR DAMAGE

	MULTIPARAS 539	PRIMIPARAS 461
L. Pubococcygeus m.	17%	14%
R. Pubococcygeus m.	21%	20%
L. Iliococcygeus m.	5%	3%
R. Iliococcygeus m.	5%	2%
Total levator damage	37%	29%
Retrodisplacement	21%	21%

Summary

A method employed recording in an anatomical order pelvic tissue damage due to parturition is presented with a preliminary report of figures showing damage to the various planes and regions. Hazards in accurately observing damage are recognized, particularly of vaginal wall detachments, cystocele and rectocele. Subinvolution constitutes the main hazard and an effort at correction was made.

Conclusions regarding the controversial subject of routine episiotomy were avoided at this time because of an insufficient number of cases. Suffice it to say that both those with and without episiotomy suffered damage. Protagonists of either procedure need more detailed and objective evidence in order that unified thought and practice may benefit the parturient woman.

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1103 GRAND AVENUE

Discussion

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—I have read of these structures in books of anatomy, I have seen some of them in dissection, but I have never before realized that it is possible to identify these individual injuries and defects in anatomic structure in the puerperal patient. I am convinced that this very thing has been done by Dr. Gainey and that this very excellent paper is a record of patient and laborious achievement. I have thought over this paper many times, and now as I correct my discussion of it, I feel convinced that this presentation is an important contribution to obstetric and gynecologic literature.

imizing damage will, we hope, be forthcoming. To date it does not seem that episiotomy offers a guarantee against damage to the levators but that the trigone is protected. The attachments of the vagina by its paravaginal adventitious tissue to the heavier fascial structures of levators and upper pelvic floor are protected from unnecessary distention and elongation by incision of the perineal outlet.

Our interpretation of damage to levators, if correct, suggests a possibility that it is irreparable from a reconstructive standpoint although not necessarily serious in its limitation of normal pelvic diaphragm function. Interpretation of damage to the upper pelvic floor apparently must wait for senility to make itself manifest in the majority of cases other than those of congenital defects.

The most serious and permanently disabling damage on the functional side in reasoning from our present observations is not to the levators or trigone but from detachment of the vaginal tube from its paravaginal attachments.

A REPORT OF THE CESAREAN SECTIONS DONE AT THE PHILADELPHIA LYING-IN-PENNSYLVANIA HOSPITAL*

ROY W. MOHLER, M.D., PHILADELPHIA, PA.

(From the Philadelphia Lying-in-Pennsylvania Hospital, and the Gynecological Department of the Jefferson Medical College)

THE present Philadelphia Lying-in-Pennsylvania Hospital was opened on July 1, 1929, and, up to March 1, 1942, 27,829 babies were delivered in the institution. The operative incidence for all deliveries was 63.2 per cent, when all but spontaneous births were considered operative deliveries. The maternal mortality for the period from July 1, 1929, to March 1, 1942, was 0.4 per cent for all deliveries and in the last one and one-half years, it was slightly less than 0.2 per cent. The neonatal and stillbirth rate has been 5.3 per cent and the corrected infant mortality rate has been 2.5 per cent for an eleven-year period ending in January, 1942. In the last one and one-half years, the infant mortality rate has been 3.1 per cent without correction.

This report includes all the cesarean sections done at the Philadelphia Lying-in-Pennsylvania Hospital in Philadelphia during the ten-year period from July 1, 1932, to July 1, 1942. This period was chosen because it would include the work at the institution during the current period and the constant work of a group of obstetricians, over two five-year periods.

The cesarean sections noted in this report have been done under the direct supervision of some member of the attending staff. In many instances a senior member of the staff would assist a junior member of the attending staff or a house officer. The aim of the whole organization has been to allow men to qualify themselves by experience, but until their competence was proved they were not given the responsibility of working without adequate supervision of one of the better trained men. This rule has applied to private as well as ward cases, and has been adhered to very closely. In most instances the cesarean sections have been done after the necessity for the operation was agreed upon by

*Presented, by invitation, at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10 to 12, 1942.

and a posterior segment. The anterior segment normally measures about 9 cm., the posterior segment about 7 cm. Now, if the anterior segment of the outlet is contracted because of some peculiar formation of the pubic arch, the child will have to be born at a greater expense to the posterior segment, and therefore more damage will result to the soft parts of this segment and perineal lacerations are likely to be more extensive. However, if the posterior segment is contracted, the child is born at the greater expense of the anterior segment, and then the injuries will be more extensive in the anterior vaginal wall and result in a greater incidence of cystocele formation.

Marion Sims long ago observed that complete lacerations of the perineum very seldom were accompanied by cystocele. The reason for it was not well understood at that time.

The configuration of the outlet of the bony pelvis has a practical bearing on the management of a case in labor. Whenever there is an evident contraction of the posterior segment of the outlet, a thorough "ironing out" of the soft tissues or an episiotomy should be done before the tissues are too greatly damaged. Conversely, if the fetal head promises to deliver at the expense of the anterior segment, episiotomy is hardly necessary, because the injury to the soft parts of the posterior segment is less likely to occur.

In order to make this study more complete, Dr. Gainney will have to go a step further and investigate the position of the fetal head and correlate it with the injuries to the pelvic floor. Obviously, occipitoposterior is likely to induce greater damage to the structures than occipitoanterior position. Again the duration of labor is likely to be a factor in the production of injuries to the soft parts.

DR. LOUIS E. PHANEUF, BOSTON, MASS.—Dr. Gainney's presentation stresses the importance of postnatal care which has come into use later than prenatal care and which is one of the great advances in obstetrics. The amount of injury should be determined immediately after labor, and not some months later, when the woman presents herself as a gynecologic patient. In this series, the damage to the pubococcygeal muscles has been greater than I had supposed it ordinarily to be.

This brings up a practical point which is that in subsequent repair, the approximation of the crura of the pubococcygei muscles, to narrow the genital hiatus, is very important. One would, however, not expect to diagnose an enterocele at such an early examination, as this occurs in the course of time through abdominal pressure directed against a deep cul-de-sac of Douglas.

Another point is gained from this presentation, namely that if we expect to get satisfactory results from our repair operations in gynecology, we must do them before these important muscular and fascial structures have undergone too marked atrophy. If the repair is done early, before the atrophy has become too pronounced, we should expect fewer recurrences.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—This presentation is not only an argument for or against episiotomy. It points out all of the damage that a normal labor produces. This damage is practically all second stage damage—a part of the labor which we, with the exception of Dr. Potter, accept. This calls particular attention to the need of watching for the full bladder at the time of full dilatation of the cervix. It points also to a lot of questions, such as analgesia or anesthesia in the second stage, or perhaps the stimulation of labor pains.

DR. GAINNEY (closing).—Our goal is to apply in our work practical interpretations, but to date this objective has been overshadowed by an effort to develop a method of analysis of soft tissue damage due to parturition. As the number of cases in the individual groups becomes larger, conclusions as to methods of min-

the policy of the staff of the hospital is to give all patients the opportunity for sterilization at the time of the second cesarean operation. The ratio of primiparas to multiparas has changed considerably over the two periods, because during the second period more patients came to the hospital because of accidents which had occurred with the first pregnancy and labor which had terminated in the death of the child.

TABLE II. OBSTETRIC HISTORIES OF PATIENTS

	PRIMIPARAS	SECUNDIPARAS	MULTIPARAS (2+)
Total number of cases 1,322	508 38.4%	419 31.7%	395 30.0%
First period, 7/1/32 to 7/1/37 665	334 50.2%	185 27.8%	136 20.5%
Second period, 7/1/37 to 7/1/42 657	174 26.5%	237 36.0%	246 37.4%

Table III shows the chief indications for section for the whole period and the first and second periods. The indications are the usual ones in most instances, the main ones being disproportion and previous section. The totals of these two indications are about the same for both periods, being 65.2 and 61.0 per cent, respectively. This occurred because a previous cesarean section was usually considered a definite indication for a subsequent operation without proving that a disproportion did, or did not, exist. Disproportion, which is relative, occurred frequently in this

TABLE III. CHIEF INDICATIONS FOR OPERATIONS

	WHOLE GROUP	FIRST PERIOD	SECOND PERIOD		WHOLE GROUP	FIRST PERIOD	SECOND PERIOD
Totals	1,322	665	657	Uterine inertia	8	7	1
Disproportion	534 40.4%	315 47.5%	219 33.3%	Ovarian cyst	7	4	3
Previous cesar- ean section	299 22.2%	117 17.7%	182 27.7%	Brow or face presentation	4	3	1
Placenta previa	84 6.4%	40 6.0%	44 6.7%	Bicornate uterus	4	3	1
Toxemia	66 5.0%	43 6.5%	23 3.5%	Obtain living child	3	2	1
Premature separation	46 3.4%	19 3.0%	27 4.1%	Acute appendi- citis	3	2	1
Heart disease	36 3.5%	19 3.0%	17 2.2%	Uterine rupture	5	2	3
Fibroids	35 3.3%	13 2.0%	22 4.0%	Tuberculosis	4	2	2
Cervical dystocia	33 5.2%	10 1.5%	23 4.0%	Post mortem to save baby	3	1	2
Previous vag- inal repair	24 2.2%	9 1.5%	15 2.1%	Abdominal preg- nancy	2	1	1
Elderly primip- aras	19 1.4%	14 2.0%	5 0.8%	Pyelonephritis	8	0	8
Transverse lie	10	4	6	Imperforate anus opening into vagina	1	0	1
Sterilization	8	6	2	Unclassified. Not of obstetric importance	76	29	47

more than one member of the staff. This report represents the work of a group of men working as a unit to do what in their judgment seemed best at the time.

TABLE I. INCIDENCE OF CESAREAN SECTION

	DISTRIBUTION OF CASES			CESAREAN SECTIONS		
	TOTAL ADMIS- SIONS	PRIVATE	WARD	TOTAL	PRIVATE	WARD
Ten-year period 7/1/32 to 7/1/42	22,754	8,190	14,564	1,322 5.8%	785 9.58%	537 3.6%
First five-year period 7/1/32 to 7/1/37	11,445	3,188	8,257	665 5.8%	325 10.2%	340 4.2%
Second five-year period 7/1/37 to 7/1/42	11,309	5,002	6,307	657 5.8%	460 9.2%	197 3.1%
One and one-half-year period 1/1/41 to 7/1/42	3,307	1,748	1,559	187 5.66%	133 7.6%	54 3.4%

Table I shows the distribution of cases on the private and ward services over the whole ten-year period. This ten-year period is analyzed in two five-year groups designated as the first period from July 1, 1932, to July 1, 1937, and the second period from July 1, 1937, to July 1, 1942. The distribution of cases is also shown for the period from Jan. 1, 1941, to July 1, 1942, to show better the current distribution of cases, and the incidence of operation. During the whole period there were many more patients on the ward service than on the private service. During the second five-year period the ratio of ward patients to private patients changed and during the last one and one-half years there have been more patients treated on the private service.

During the whole ten-year period, 1,322 cesarean sections were done, 785 operations, or an incidence of 9.3 per cent, were done on the private service and 537, or an incidence of 3.6 per cent, were done on the ward service. Fortunately for comparison the number of operations were about the same during both five-year periods, and the incidence of operation, 5.8 per cent, was the same for both periods.

The incidence of cesarean sections for the whole group is higher than many reports studied and is about twice the incidence occurring in the whole Philadelphia area as reported by the Committee on Maternal Welfare of The Philadelphia County Medical Society for a comparable time. The incidence of the operation on the ward service, however, corresponds closely to the reports given from other institutions.

The incidence of cesarean sections on the private service for the first period was 10.2 per cent, and for the second period it was 9.2 per cent, and for the period from Jan. 1, 1941, to July 1, 1942, it was 7.6 per cent. The incidence is high because of the selected group of patients which are referred to the hospital, particularly on the private service, and because of the liberal view taken by the staff toward the operation. The view taken by the staff is that when sections are indicated and performed by experienced gynecologic and obstetric surgeons it is a relatively safe and satisfactory procedure for the patient and for the physician.

Table II shows the obstetric histories of the patients for the whole series of 1,322 cases, and for the two five-year periods. A parity of more than two is not specified because it has no particular significance in this report. Most of the patients were primiparas and secundiparas, because

in the table when it is observed how few patients had ruptured membranes for a period longer than twelve hours. Rupture of the membranes has been considered an absolute indication for a low cesarean section or a Porro operation, depending upon the length of time over which the membranes have been ruptured and the evidence of infection.

Table VI is a study of temperature morbidity during the second period of this report. Until April, 1940, our standard of temperature morbidity was a "temperature of 100° F., or over, twice in any twenty-four hours excluding the first twenty-four hours after delivery, operation, or admission." With this standard as a basis, the temperature morbidity was 59 per cent. The new standard for temperature morbidity is the one recommended by the Maternal Welfare Committee, and, since its adoption, there have been 245 patients delivered by cesarean section with a temperature morbidity of 22 per cent, which is within expected and normal range. The patients operated upon during the first period of this study were not included in this table, because it was thought that they would show nothing according to the present standards of morbidity.

TABLE VI. STUDY OF TEMPERATURE MORBIDITY (SECOND PERIOD)

	OLD STANDARD	NEW STANDARD
Total patients operated upon	412	245
Total morbidity	247—59.0%	54—22.0%
Causes of morbidity		
Postoperative reaction	128—30.0%	22— 9.0%
Endometritis	35— 8.7%	14— 6.0%
Sapremia	23— 5.5%	1— 0.5%
Wound infection	8— 2.0%	5— 2.0%
Pyelitis	35— 8.7%	6— 2.4%
Pneumonia	8— 2.0%	3— 1.2%
Phlebitis	8— 2.0%	0—
Breast engorgement or infection	2— 0.5%	3— 1.2%

Table VII shows the maternal mortality for the various periods on the private and ward services. For the entire group of 1,322 patients, there were 26 maternal deaths, or an incidence of 1.96 per cent. During the first period, there were 17 maternal deaths, or an incidence of 2.55 per cent. During the second period, there were 9 maternal deaths, or an incidence of 1.37 per cent. During the periods compared, there was little change in the maternal mortality on the ward service, but there was a marked drop in the maternal mortality on the private service. The patients having cesarean section on the private service from July 1, 1942, numbered 460, with 3 maternal deaths, or an incidence of 0.65 per cent. It is difficult to explain the rather high incidence of 3.0+ per cent of ma-

TABLE VII. MATERNAL MORTALITY

NUMBER OF CASES	PRIVATE	DEATHS	WARD	DEATHS	TOTAL DEATHS
1,322	785	9	537	17	26
7/1/32 to 7/1/42		1.15%		3.17%	1.96%
First period	325	6	340	11	17
665		1.84%		3.23%	2.55%
7/1/32 to 7/1/37					
Second period	460	3	197	6	9
657		0.65%		3.00%	1.37%
7/1/37 to 7/1/42					

group of patients, and its existence may be a question by some. Placenta previa and premature separation of the placenta was regarded as an indication for cesarean section in almost all instances where it occurred and the incidence was about the same during both periods. Toxemia had become a much less frequent indication for cesarean section in the second period and indicates plainly the reduced incidence of the malady and the change in the management of the condition. The other indications have occurred infrequently and in some cases the procedure in management may not seem to be the one that would be chosen by some.

Table IV lists the types of cesarean sections which were done during the ten-year period and during the first and second five-year periods. During the whole period of this report, 71.84 per cent of the patients had classical operations and there were slightly more of the classical operations in the second period than in the first. In most large clinics the tendency has been for the low type operation and it is rather interesting to observe that the incidence of the low type operation had diminished

TABLE IV. TYPES OF CESAREAN SECTIONS

	TOTAL	CLAS- SICAL	KERR	BECK	PORRO	WA- TERS	NOT STATED	STERIL- IZATION
Ten-year period 7/1/32 to 7/1/42	1,322	949 71.8%	256 19.4+%	68 5.1+%	34 2.5+%	2	13 1%	408 30+ %
First period 7/1/32 to 7/1/37	665	461 71.1%	127 19.0+%	53 8.0+%	14 2.0+%	0	10 1.5+%	178 27.0%
Second period 7/1/37 to 7/1/42	657	488 74.3+%	129 20.0+%	15 2.3+%	20 3.0+%	2	3	230 35.0%

rather than increased during the second five-year period. For a period of one year, during 1936 and 1937, the Kerr type operation was done almost routinely. The results during that year showed no variation from the results which had been secured previously and for that reason the tendency seemed to be toward fewer low type operations. The attitude of the staff now toward low sections seems to be that patients who have been in labor over twelve hours and patients with ruptured membranes or potential infection should have a low type cesarean section or a Porro type operation. In perfectly clean and elective cases, it is thought unnecessary to do anything more than a classical operation. Most sterilizations were done on patients who had had more than one cesarean section and the method used for sterilization was the Pomeroy modification of the Madlener operation.

Table V shows the time and the number of patients who were in labor and the number of patients with ruptured membranes. Usually an effort was made to avoid a cesarean section after rupture of the membrane, and this accounts for the few patients who were operated upon after the membranes had ruptured. This attitude is demonstrated very clearly

TABLE V. RECORD OF LABORS

LENGTH	PATIENTS IN LABOR		MEMBRANES RUPTURED	
	FIRST PERIOD	SECOND PERIOD	FIRST PERIOD	SECOND PERIOD
1-12 hours	107	109	42	44
12-24 hours	64	43	5	25
24-48 hours	34	27	5	12
48+ hours	5	11	8	4

TABLE VIII. ANALYSIS OF DEATHS

YEAR	SERV- ICE	AGE	PARA	PREV. C. S.	INDICATION	TYPE C. S.	LABOR	MEMB.	EXAM.	ANES.	CAUSE OF DEATH	WEIGHT OF CHILD	SEX OF CHILD	CHILD RE- SULTS
First Period														
1932	P	22	i	0	Contracted pelvis disproportion	B	5½ hr.	0	2 Vag.	G & E	Post-partum shock and collapse	8-3¼	F	Lived
1933	P	29	i	0	Myoma uteri, tox- emia disproportion	C	0	0	1 Vag.	G & E	Peritonitis, pul- monary embolism	6-0	F	Lived
1934	W	34	iv	3	Chronic nephritis, previous C. S.	C	0	0	0	E	Lobar pneumonia	4-1	F	Lived
1934	W	33	iv	0	Toxemia, dispropor- tion	C	0	0	0	G & E	Peritonitis	11-5½	F	Lived
1934	W	32	iv	2	Ruptured uterus 5 hr. before de- livery	P	0	0	1 Rec.	G & E	Postoperative shock	6-8	F	Died
1934	P	26	ii	0	Membranes rup- tured 5 days, at- tempted vaginal delivery	P	10½ hr.	4 days	1 Vag.	G	Operative shock during manipu- lation			Dead
1935	W	44	xiv	0	Placenta previa	C	0	0	1 Vag.	E	Pneumonia on 5th P.O. day	7-5¼	F	Lived
1935	P	40	i	0	Disproportion, old primipara	C	0	0	0	G & E	Peritonitis	6-2	F	Lived
1935	P	29	i	0	Placenta previa; auto accident	B	3½ hr.	Yes	1 Vag.	G & E	Postoperative shock	6-12½	F	Lived
1935	P	29	ii	1	Disproportion and previous section	C	0	0	0	G & E	Pulmonary embolism on four- teenth day	7-10¼	M	Lived
1936	W	19	i	0	Severe T.B., ter- tiary syphilis	C	0	0	0	Local	Died in 5 days; T.B.	3-1½	M	Died in 9 hr.
1936	W	19	i	0	Contracted pelvis, disproportion	K	24½ hr.	16 hr. +	3 Rec.	G & E	Peritonitis	7-6½	M	Died 20 days after opera- tion

ternal mortality on the ward service, and one can conjecture as to why they occur, but all the explanations do not hold in each instance. When these deaths are analyzed more carefully we may find an explanation.

Table VIII shows a tabular analysis of the 26 maternal deaths. Sixteen deaths, or a mortality of 1.67 per cent, followed 949 classical operations; 5 deaths, or a mortality of 11.7 per cent, followed 34 Porro operations; 3 deaths, or a mortality of 1.19 per cent, followed 256 Kerr operations; and two deaths, or a mortality of 3 per cent, followed 68 Beck operations. During the first period there were 6 deaths, due to shock and in the second period there were 5 deaths due to shock, a total of 11. Six of these 11 deaths were apparently accidents which occurred and could have been prevented. The operation, however, was the factor which was accepted as the cause of death, but one cannot be sure that the anesthetic, which was gas and ether in each instance, was not the responsible factor.

Three of the 11 patients who died of shock had either placenta previa or premature separation, one had a ruptured uterus, and one died during cesarean section following a traumatic attempt at vaginal delivery. The type of operation seemed to have no bearing on the outcome.

During the first period there were 4 deaths from peritonitis and one from peritonitis and pulmonary embolism, and during the second period there was 1 death from peritonitis. Two of the deaths from peritonitis followed the Porro operation, 3 followed the classical, and one followed the Kerr operation.

Pulmonary embolism accounted for 3 deaths, one of these noted above had peritonitis, and cerebral embolism accounted for one death.

There were 3 post-mortem cesarean sections: One patient died of Avertin anesthesia before the operation was begun and a post-mortem cesarean section was done in an effort to save the baby. Another patient died of bronchopneumonia about six weeks before term. A third patient died of placenta previa two and one-half weeks before term, and a post-mortem section was done to save the child, without success.

One patient died of eclampsia and convulsions twenty-four hours after delivery by cesarean section, because it was thought immediate delivery was necessary.

One died of pneumonia and nephritis after delivery; the nephritis had been present when pregnancy occurred, and she had had a previous section.

Another patient died of pneumonia on the fifth postoperative day.

When these deaths are analyzed according to the standard suggested by Schumann, we find that 9 of the patients died from causes complicating pregnancy and labor, or other systemic conditions, and that the method of delivery could not have been a factor in the cause of death. There are many interesting data which can be discussed in regard to the maternal mortality which occurred among these patients. Some of these deaths should not have occurred, and in retrospect and in staff conferences, where they were always discussed critically, the errors, when they existed, were attributed to the responsible person. These deaths were also analyzed by the Philadelphia Maternal Mortality Committee and the factor responsible for the cause of death was determined.

As others have said, and it seems to be pertinent here that a study of maternal mortality connected with cesarean section or a critical attitude toward the high incidence of cesarean section will not change the judgment of an individual when he is faced with the decision of how best to try to save the life of a mother and a child. The training, experi-

ence and capabilities of the individual will influence his judgment, and, if it is his judgment that cesarean section is the best method, preaching will not change it. The reputation of the individual is built on the soundness and acceptability of his judgment.

Anesthesia

In this report we have not tabulated the type of anesthesia. Generally the anesthetic was nitrous oxide plus oxygen through a closed mask supplemented with enough ether to avoid straining or asphyxiation of the patient. Within the last one and one-half years, open drop ether anesthesia following nitrous oxide and oxygen induction has been usually used.

The group at the Lying-in-Hospital believe that the routine anesthetic has not been ideal or quite satisfactory, and an effort to improve it has been made. Within the last nine months the prejudice against spinal anesthesia has been overcome, and it has been used on a number of patients, with very satisfactory results. The method used has been the fractional technique and as little as 75 mg. of novocain has been adequate with some patients, usually 150 mg. is the necessary dose. At times local novocain, avertin, or vinethene have been used as anesthetics; none of these have been used often enough to report on the results.

TABLE IX. RECORD OF INFANT MORTALITY

PERIOD	SINGLE BIRTHS	TWINS	TOTAL CHIL-DREN	STILL-BIRTHS	NEO-NATAL PREMA-TURE	NEO-NATAL OTHER CAUSES	TOTAL	LIVING CHIL-DREN
7/1/32 to 7/1/42	1,310	12	1,334	30	49	34	113 or 9.2%	1,221
First period 7/1/32 to 7/1/37	657	8	673	19	30	20	69 or 10.25%	604
Second period 7/1/37 to 7/1/42	653	4	661	11	19	14	44 or 6.6%	617

Table IX shows the record of infant deaths for the whole period and for the first and second periods. There were 1,310 single births and 12 sets of twin births. Among these were 113 deaths, or an incidence of 9.2 per cent. Thirty of these infants were stillborn and 83 were neonatal deaths. Many of the neonatal deaths were among the pre-matures which were delivered by cesarean section because of placenta previa and premature separation of the placenta; it is obvious that the method of delivery had no bearing on the incidence of death among these infants. During the second period of this report, the infant death rate showed an incidence of 6.6 per cent which is about 40 per cent less than the infant death rate in the first period. This 6.6 per cent infant death rate is about twice the incidence of the infant deaths for all the babies delivered in the hospital for the last one and one-half years. This increased infant death rate cannot be attributed to the method of delivery, but could very often be ascribed to the complication which made the cesarean section necessary.

Discussion

This report has been submitted because it represents a rather large group of patients who have been delivered by cesarean section in a large

1936	W	19	ii	i	Previous section, contracted pelvis, disproportion	G			0	G & E	Shock and hemorrhage on table	3-4	F	Lived 2 hr.
1936	W	30	iii	0	Fulminating eclampsia	G	0	0	0	Local	23 convulsions, died within 24 hr., eclampsia	3-12	F	Still-born
1936	W	41	iii	0	Twisted ovarian cyst	P	0	Artificially ruptured	1 Rec.	G & E	Peritonitis, died third P.O. day	7-5½	F	Lived
1937	W	21	i	0	Disproportion	K	27½ hr.	27	2 Rec. 3 Vag.	G & E	Postoperative shock in 4½ hr.	9-4	M	Lived
1937	W	34	iii	0	Post mortem in an attempt to save child; bronchopneumonia	PM G	0	0	0	None	Before operation	3-1	F	Still-born

Second Period

1937	W	24	iii	0	Disproportion, previous C. S.	C	4 hr.	0	2 Rec. 1 Vag.	G & E	Shock during operation or anesthetic?	7-14½	M	Lived
1937	P	34	iv	0	Previous extensive plastic	C PM	0	0	0	Avertin	Avertin anesthesia death	9-12	M	Died
1938	W	38	iii	0	No advance in labor	P	20 hr.	0	4 Rec. 4 Vag.	E	Peritonitis on ninth day	10-2½	M	Still-born
1938	W	31	iv	0	Placenta previa	G PM	0	0	1 Vag.	G & E	Respiratory failure before section was started		M	Still-born
1939	W	35	iv	0	Plastic and sterilization at 1 month	G	0	0	1 Rec.	G & E	Pneumonia	7-7¼	F	Lived
1939	W	24	iii	0	Previous C. S.	P	5 hr.	0	0	G & E	Shock during operation	7-4	M	Lived
1940	P	36	i	0	Cervical dystocia after 24 hr. labor	G	24 hr.	0	3 Rec. 2 Vag.	G & E	Intrapartum uterine bleeding	8-7	F	Lived
1941	P	23	i	0	Cervical dystocia	K	18¼ hr.	0	1 Rec. 2 Vag.	G & Vincthene	Cerebral embolism fourteenth P.O. day	8-3	M	Lived
1942	W	18	i	0	Premature separation	C		0	0	No + O₂	Shock during operation	7-7	M	Still-born

Discussion

DR. LOUIS E. PHANEUF, BOSTON, MASS.—The study of 1,322 cesarean sections is of great value and may permit certain conclusions. Dr. Mohler mentioned the incidence which he feels is high, and yet, compared with that of other clinics, it might not be considered so.

The indications presented for cesarean section, in the main, were disproportion, previous cesarean section, placenta previa, and premature separation of the placenta. These correspond with the indications reported in other large series.

There are some differences of opinion in the employment of cesarean section in premature separation of the placenta which has been especially noticeable in the last decade. Many of these patients can be safely delivered through the pelvis, using cervical and vaginal tamponade after rupturing the membranes, applying a tight abdominal binder by means of a Spanish windlass or by other means. This causes more worry for the obstetrician during labor, but he may be recompensed by a quicker recovery of his patient. The decrease of cesarean sections in toxemia is in keeping with the present thought in obstetrics.

The paper draws attention to a decrease of the low cesarean section against the classical cesarean section during the last five-year period. The tendency in many clinics has been the opposite, that is, the increase has been in favor of the low cesarean section. The reasons given for the performance of the low cesarean section are twelve hours of labor, ruptured membranes and presumable infection. In this type of parturient, the low cesarean section certainly should be safer than the classical operation.

Other observers have made comparisons between the low and classical cesarean sections, and conclusions have been drawn that there is not much difference in their safety. To me the difference is marked. I am convinced of the increased safety of the low over the classical cesarean. If the low cesarean is safer for the individual who has had twelve hours of labor, ruptured membranes, etc., by the same token it should be safer for every woman who is subjected to an abdominal delivery.

The increased difficulties of the low operation are mentioned. It merely means the separation of the bladder, a simple procedure, and we have had no difficulty in teaching this method to residents.

Noteworthy in the paper is the lack of use of the extraperitoneal cesarean section which has increased the safety of abdominal delivery. The adoption of this method in my own work has reduced the incidence of cesarean-hysterectomy in the presence of presumable or existing infection. Formerly I did a number of Porro cesarean sections, having reported a series of 25 such operations without maternal mortality in 1931. With the advent of the extraperitoneal cesarean section, I have reserved cesarean-hysterectomy for women with uterine fibroids.

The death rate in this large series of cases reported by Dr. Mohler is not excessive. Unfortunately there will always be a death rate in cesarean section, the deaths frequently being due to the existing pathology for which the operation was performed, rather than to the operation itself. If a woman, with a certain pathologic lesion is delivered through the pelvis and dies, the death is usually ascribed to the pathologic lesion rather than to the method of delivery. On the other hand, if she is delivered by cesarean section, her death is ascribed to the operation. It is obvious that this method of reporting cases never results in favor of cesarean section.

The shock mentioned in connection with these patients can be overcome in most instances nowadays by the administration of blood plasma which is readily available. Although my experience with the use of the sulfa drugs is somewhat limited, I have found that they have reduced the morbidity to a considerable degree.

DR. IRVING W. POTTER, BUFFALO, N. Y.—Our series of cesarean sections covers something over 3,000 cases, but our maternal mortality is a little under 3

obstetric clinic by obstetricians and gynecologists of various training and capabilities. The report has been given in enough detail to determine what changes will be necessary in the management of some of our cases in the future.

The only divergence of this report from other comparable reports seems to be the incidence of the cesarean sections and the low proportion of the so-called low type operation. This is partly explained under Table IV but more explanation and discussion may be in order. Many men qualified to do obstetric and gynecologic surgery can do a low type operation with absolute confidence and safety. However, a large hospital staff is made up of individuals with various capabilities and experience. There are men on the staff who are especially capable to manage difficult vaginal deliveries and some of these men may not be especially interested or qualified in doing anything but simple surgery.

It is my belief that the low type cesarean section is a more difficult operation than the classical operation, and no one but an experienced obstetric surgeon should do them. An inexperienced surgeon subjects a patient to a greater danger in doing a low section than a classical operation on an elective case.

Summary

The tables and discussions have been given with an idea of showing the number, incidence, method, and results of 1,322 cesarean sections done in a large clinic during the past ten years.

Two five-year periods of work have been compared with the idea of seeing what changes occurred.

1. The report has demonstrated that the private service has increased during the second five-year period, and that the incidence of cesarean section has dropped on the private service.

2. The chief indications for cesarean sections have remained about the same.

3. The types of cesarean section have varied considerably but the tendency is toward the classical operation. There seems to have been no maternal mortality or morbidity which could be directly ascribed to the type of operation performed.

4. The maternal mortality rate was low for the 1,322 cases, an incidence of 1.96 per cent. During the second period of this report, it was 1.37 per cent for both private and ward services and during the second period of this report it was 0.65 per cent for 460 private patients.

5. The infant mortality rate was high during the first period of this report and showed considerable drop in the second period.

6. Finally, this report shows that the attitude toward cesarean section has changed some during two five-year periods, and that the results from the work have improved but still leaves something to attain.

I wish to thank Drs. Norris W. Vaux, Clifford B. Lull, Robert A. Kimbrough, and other members of the staff of the Philadelphia Lying-in-Pennsylvania Hospital for the privilege of using the records of their private patients which have been included in this report.

over the web between the thumb and index finger, has demonstrated how common periods of anoxia not shown by the conventional signs are during anesthesia. Seven minutes' deprivation of oxygen is sufficient to cause the death of stellate cells and the cells of Purkinje. The operator should never permit a degree of cyanosis sufficient to darken the blood in the wound to continue.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I would like to know why in all of these studies of cesarean section there is such a definite distinction made between private and ward cases? It seems to me that they had better be put on the same basis. We do not divide carcinoma cases on this basis. Why should we make any distinction for cesarean sections?

DR. MOHLER (closing).—In reply to Dr. Kennedy's remarks, Fig. 1 shows the maternal deaths and the incidence of cesarean section in the Philadelphia area during a ten-year period. In 1931 there was about a 6 per cent maternal mortality

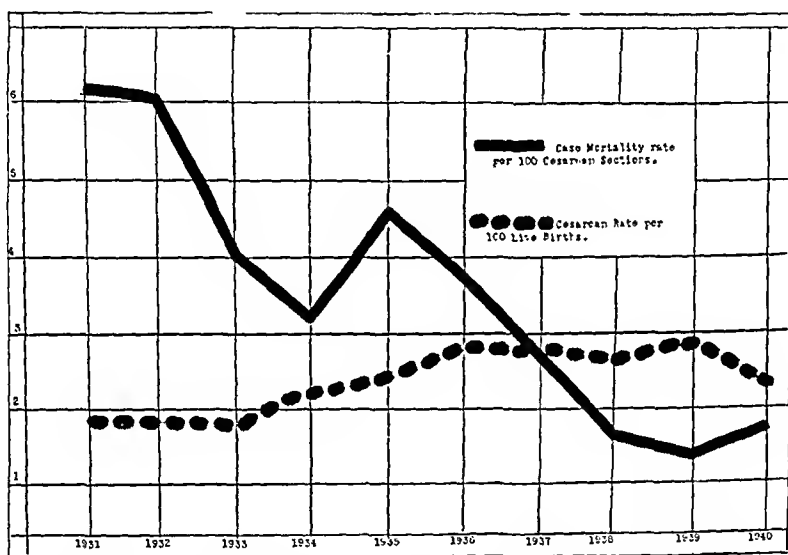


Fig. 1.—Cesarean section mortality in Philadelphia, 1931 to 1940. (Courtesy of Philadelphia Maternal Mortality Committee.)

from cesarean sections in the Philadelphia area. Since then the maternal mortality has dropped until in 1940 it was a little less than 2 per cent. The incidence of cesarean sections during the period of my report has increased almost 50 per cent in the Philadelphia area and during the same period the maternal mortality for cesarean sections has dropped two-thirds. It seems, therefore, that in spite of the fact that we are doing more cesarean sections, the incidence of maternal mortality has been lowered considerably.

In regard to Dr. Babcock's remark, some of the patients who supposedly died from shock were probably the victims of badly administered or wrongly selected anesthesia. I agree thoroughly with Dr. Babcock, and we have been trying to be more selective in our choice of anesthetic. Recently we have been doing a number of cesarean sections under spinal anesthesia with excellent results. We have not had enough experience to report but so far we are enthusiastic.

Dr. Kosmak has questioned the justifiability of reporting cesarean sections separately in reference to the ward and private services. The answer is evident in the report which shows the differences in the two services. The reason for this contrast cannot be a part of this report but should be studied.

per cent for all types of cases. Now we have done practically no procedures but the so-called "high" operation. The rupture of the membranes after twelve hours of labor and vaginal examination have not had anything to do with our selection of type of operation. We feel that an operation that is above the navel is preferable because it is quicker; you can pack the uterus from above in potentially infected cases and can get the pack out in the first twenty-four hours and your patient does very well. In infected cases we would rather remove the uterus, and we do that before the removal of the baby which is an advantage in many ways. It is simpler, there is less loss of blood, and our patients do well. Altogether we have got along very well with confining our efforts to one type of operation.

DR. JAMES W. KENNEDY, PHILADELPHIA, Pa.—What I have to say in regard to cesarean sections in general, is in no way a criticism of Dr. Mohler's report. Cesarean section is the easiest operation to perform of all major abdominal surgery, and today it is too much enjoyed by an overenergetic profession. It is my opinion that over 95 per cent of cesarean sections performed tomorrow throughout the country *could have been deliveries by the birth canal.*

During my young and energetic days when I had charge of the Joseph Price obstetric course which was conducted in the slums of Philadelphia, I sent 50-odd patients to the Joseph Price Hospital for cesarean section. I was ordered by my old master to scrub my hands and deliver the supposed candidates for cesarean section. I did and but one patient had a cesarean section.

There is a postoperative history in cases of cesarean section which should be considered by every conscientious physician. To place a scar in the uterus and abdomen of a young woman during her first childbirth is to suspend a guillotine over her neck for the rest of her life. Where will she be during her next labor; will she fall in the hands of an accomplished surgeon, or will she die from a ruptured uterine scar?

We must have fewer cesarean sections and the mortality must approach that of normal labor in elective cases. We must also remember that every abdominal scar, as well as the uterine scar, carries a potential danger of postoperative bowel obstruction for the rest of the patient's life and the adage, once a cesarean always a cesarean, has weight. The obstetric woman is some one's patient from the cradle to the grave, and she is the greatest resource of the human race.

DR. J. BAY JACOBS, WASHINGTON, D. C.—I feel that the incidence of cesarean section as presented by the essayist is very high, particularly among private patients. Last year I reported about 740 cases that were classified as borderline, these representing one-twelfth of the total material. Cesarean section was performed in only 6 per cent of our borderline cases.

The fact that cesarean section is easy to do and so considered by a large group of obstetricians, is certainly no indication for its performance. It would be interesting to know in what proportion of patients operated upon for disproportion, x-ray pelvimetry had been used? Roentgenographic pelvimetry is recognized as one of the essentials preliminary to the performance of cesarean section in borderline cases.

DR. W. WAYNE BARCOCK, PHILADELPHIA, PA.—I cannot forbear a word regarding deaths reported as from shock during operation, because we now have evidence that if there has been no excessive hemorrhage or traumatism during operation, such deaths are usually anesthetic deaths, due really to anoxemia, a common complication particularly since cyclopropane has been popularized.

A number of fatalities have occurred at the Philadelphia General Hospital which took place several days after the anesthetic was given. They would not have been recognized as anesthetic deaths had not the neuropathologist found the characteristic changes in prepared sections of the brain. McClure, using a selenium cell

cystocele or urethrocele may have severe incontinence, which perhaps is the major complaint for which they seek treatment. Cystoscopic examination in cases of severe incontinence will reveal whether the urethra is distorted or the internal sphincter is gaping or fixed.



Fig. 1.—Female urethra located behind symphysis and embedded in anterior vaginal wall.

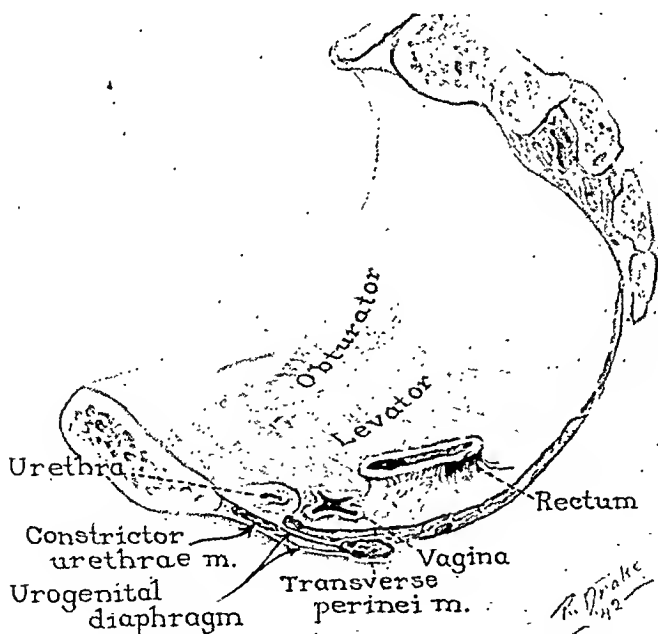


Fig. 2.—Relation of the muscles of the urethra and urogenital diaphragm (sagittal section).

Anatomy of Vesical Neck and Urethra

The female urethra measures 4 to 4.5 cm. in length. Both the urinary bladder and the urethra are surrounded by loose areolar tissue which

URINARY INCONTINENCE IN WOMEN*

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(From the Division of Surgery, Mayo Clinic)

INCONTINENCE among women has been previously investigated by eminent physicians in all countries and various surgical procedures have been recommended for its correction. My intention here is, not to review all these methods, but to emphasize the importance of a careful analysis of the cause of the incontinence and also to emphasize that a complete understanding of the anatomy of the vesical neck, urethra, and pelvic fascia plus the normal physiology of micturition is imperative before one undertakes any surgical corrective procedure. It seems to me that the very careful experimental work on this subject by Kennedy[†] has done more to clarify it than any previous contribution and I wish to elaborate and emphasize some of his suggestions because of their accuracy and fundamental importance.

Incontinence may either be congenital or acquired. In the former group it is caused by a congenital defect, the extreme of which is represented by exstrophy of the bladder. Partial epispadias usually is the most confusing because in some instances, objectively at least, the anatomic relations appear normal but on cystoscopic examination the musculature of the dorsal portion of the urethra is missing. There may be faulty development of the pelvic fascia which supports the bladder and of the musculature of the vesical neck and urethra. In spite of this, the urethra may function normally for many years, but when some atrophy develops during the menopause, various degrees of incontinence follow. One other congenital defect which must be mentioned in this connection is spina bifida. The defect of innervation may not be sufficient to produce incontinence until after a normal delivery. Here the anatomic relations of the vesical neck and urethra are undisturbed, and unless the defect is recognized surgical correction to the urethra and vesical neck will fail. Furthermore, it must be recognized that slight trauma of any type may initiate incontinence when spina bifida exists.

Acquired incontinence, in which we are primarily interested, is that seen incident to childbirth and less commonly that incident to operations for cystocele and prolapse. The incontinence may vary from moderate to severe, depending on the degree of trauma. Not all of these patients require cystoscopic examination, but a direct query regarding leakage of urine, when vaginal plastic procedures or vaginal hysterectomy is contemplated, is essential. Some patients who have complete proidentia do not have any incontinence while others who have very slight

*Read at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 10 to 12, 1942.

of the bladder this circular muscle is thickened and is called the internal urethral sphincter or sphincter vesicae. This circular muscle thins out over the outer third of the urethra and over the remaining portion of the bladder. It also, by a slight thickening at the external meatus, gives rise to what has been designated as the external involuntary urethral sphincter. There are a few inner longitudinal smooth muscle fibers (Fig. 2). These two urethral sphincters are involuntary, which is exactly the same as a smooth muscle sphincter of circular fibers anywhere else in the body. In more recent editions of *Gray's Anatomy* a striated voluntary sphincter is described. It lies between the superior and the inferior layer of the urogenital diaphragm, covering the middle and posterior thirds of the urethra (Fig. 3). It is designated the sphincter urethrae membranaceae. Its external fibers arise from the junction of the inferior rami of the pubis and ischium to the extent of 1.25 to 2 cm. and from the neighboring fasciae. They arch across the front of the urethra and bulbourethral glands, pass around the urethra and behind it, and unite with the muscle of the opposite side by means of a tendinous raphe (Fig. 4).

Innervation of the Sphincters*

The innervation of the internal vesical sphincter is still the subject of much controversy and its exact innervation has not been completely established. Until recently it was believed that there was a dual innervation of the bladder and vesical neck through the sympathetic and parasympathetic divisions of the autonomic nervous system. The former was thought to cause contraction of the internal vesical sphincter and relaxation of the detrusor and was, therefore, known as the "nerves of filling" while the latter, or parasympathetic innervation, was known as the "nerves of emptying" since it was known to cause contraction of the detrusor and relaxation of the internal vesical sphincter. Evans has seriously questioned this hypothesis recently and has presented evidence which strongly suggests that the innervation of the internal vesical sphincter is solely through the parasympathetic system. Denny-Brown and Robertson expressed the same point of view and showed that the internal vesical sphincter serves a reciprocal relation with vesical contraction, its opening depending on vesical contraction and its closure on the subsidence of vesical contraction. The function of the internal sphincter is, therefore, reflex and is not immediately under voluntary control.

Mention has not been made of the sphincter trigonalis, thought to be innervated by the sympathetic nervous system, since its role in the opening and closure of the internal vesical orifice has not been too well established. The problem is complicated still further by the fact that McCrea has found striated muscle fibers among the smooth muscle fibers of the internal sphincter, and this, if true, may be of great functional significance.

The innervation of the external urethral sphincter or compressor urethrae is through the somatic nervous system via the pudic or internal pudendal nerves and its function is to defer or postpone micturition. Denny-Brown and Robertson have presented evidence that suggests that this sphincter can be voluntarily contracted but not voluntarily relaxed. Its relaxation is apparently reflex and depends on vesical contraction

*I am indebted to Dr. C. E. Jacobson for the portion of this paper on innervation of the sphincters.

is an extension of the pelvic fascia. This tissue becomes firm and fixed at certain points for protection and support, as at the vesicouterine reflection, at the ureterovesical junction and the entire ventral surface of the urethra. The urethra is further fixed and suspended in its normal position to the pubis by the pubovesical ligament. According to Gray "the female urethra is placed behind the symphysis pubis, imbedded in the anterior wall of the vagina, and its direction is obliquely downward

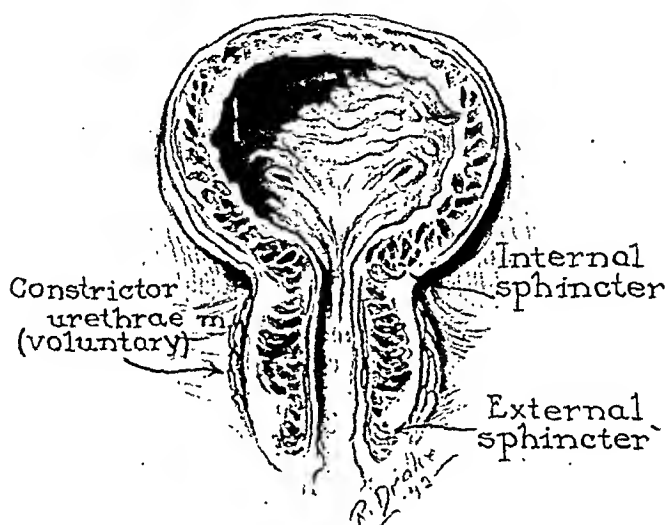


Fig. 3.—Musculature of the urethra.

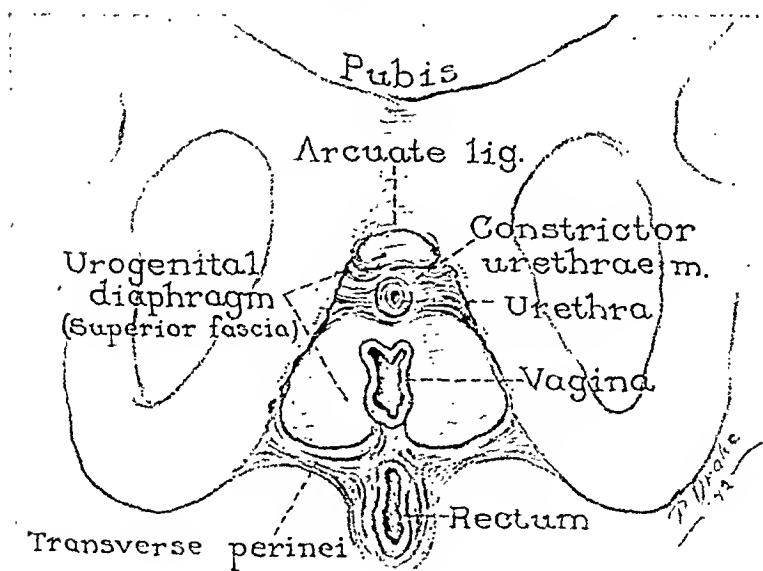


Fig. 4.—Diagrammatic view of constrictor urethrae muscle and urogenital diaphragm.

and forward; it is slightly curved with the concavity directed forward [Fig. 1]. It perforates the fasciae of the urogenital diaphragm, and its external orifice is situated directly in front of the vaginal opening."

The principal muscular coat is circular and is continuous with that of the bladder. Over the posterior third of the urethra and the neck

urethral involuntary sphincter connected by an epithelial lined tube 4 cm. in length, the incontinence was thought to be the result of damage to the internal vesical sphincter only. This may be true still in certain mild instances of incontinence but in most cases the damage extends beyond this sphincter and involves the voluntary sphincter also, which, according to Gray, surrounds the entire membranous urethra and, therefore, it covers the internal sphincter, or as Kennedy⁵ states, it reinforces the internal sphincter.

The sphincter urethrae membranacea is exactly the same in men with this one exception, that the prostate is interposed between it and the internal vesical sphincter. In men it is designated as the cut-off muscle or the external urethral sphincter. From this arrangement it is clear why incontinence does not occur when internal sphincterotomy, trans-urethral resection of the prostate, or complete enucleation of the prostate is performed, unless the sphincter urethrae membranacea is injured. Urologists, therefore, treat this sphincter muscle with extreme care and I am certain that its homologue in women deserves the same care and attention. The surgical approach in women is much simpler than in men and the technique of exposure and repair is not complicated.

Kennedy⁶ has stressed the method of injury to the sphincter mechanism that occurs during childbirth and it should be emphasized. Trauma during delivery is between the urethra and the symphysis or the inferior rami of the pubis from prolonged pressure. The internal sphincter is forcibly stretched and the voluntary sphincter is separated from its medial ventral attachment on the urethra. Distortion of the urethra or fixation of any portion of the sphincter mechanism to the pubic rami he regards as a very definite cause of incontinence. Distortion or fixation is brought about most likely from hemorrhages into the muscle and along the urethral shaft, which finally result in adhesions with shortening and fixation of the sphincter mechanism to the pubis or rami. Such deformities he has demonstrated by roentgenograms of the urethra in patients prior to surgical repair and in patients who were unimproved or made worse by surgical repair using the Kelly method.

Incontinence which comes on following a repair for cystocele, or vaginal hysterectomy for prolapse that did not exist prior to operation is very disappointing to both patient and surgeon. The sphincter mechanism was intact even though the anterior vaginal wall was down, but when the repair of the cystocele was executed the voluntary sphincter support was not replaced after being separated from the vaginal wall. This complication can be avoided if the possibility of surgically producing incontinence while repairing a cystocele or performing vaginal hysterectomy is kept in mind.

The Kennedy Operation

The cervix is grasped with a tenaculum and the anterior vaginal wall opened in the usual manner to within 1.5 cm. of the external urinary

or relaxation of the internal sphincter. Learmonth has shown that the external urethral sphincter among women is not indispensable as he has sectioned both pudic nerves and did not note any incontinence.

While the levator ani, deep perineal and bulbocavernosus muscles can hardly be considered as true sphincters they are nonetheless often spoken of as "accessory sphincter muscles" and their co-ordinated contraction or relaxation as "associated movements." Denny-Brown and Robertson stated that there is little doubt that the levator ani and perineal muscles are relaxed during micturition and that they may be thought of as having accessory sphincter control.

Comment

The first concrete evidence of this voluntary sphincter function was demonstrated by Kennedy⁴ in 1937, using a urethral bag and measuring the amount of pressure in centimeters of water which was required to overcome the sphincteric action of the internal urethral sphincter and the sphincter membranaceae under normal conditions. The information ascertained by this method, which is of extreme importance, is that the sphincter around the middle third of the urethra resisted twice as much pressure as did the internal third of the urethra. This method was then used as a diagnostic procedure for women who had incontinence and without exception the relative weakness of the membranous portion of the urethra could be demonstrated. Continence was similarly demonstrated following reconstruction of the muscular support of the middle and inner portions of the urethra. Kennedy⁵ concluded that there is an involuntary sphincter muscle about each of the inner and outer thirds of the urethra and that there is an additional sphincter about the middle third which is probably under voluntary control.

There is other direct evidence which confirms Kennedy's findings. For example, internal sphincterotomy can be performed on a woman without causing incontinence. Also, by using a panendoscope to examine the urethra and bladder, the middle third of the urethra can be seen to contract and relax voluntarily as suggested to the patient. Resection of the vesical neck and inner third of the urethra without producing incontinence would seem to me to be sufficient proof that the internal vesical sphincter is of less importance than the sphincter over the middle third. This was actually done by my colleague (Priestley) on a patient sixty years of age for carcinoma of the bladder involving the vesical sphincter. The entire sphincter and the first centimeter of the urethra were resected and the stump of the urethra was anastomosed to the bladder at the apex of the trigone. The patient remained continent up until a few weeks before her death which was due to recurrence. The final period of partial incontinence was most likely the result of local recurrence.

It is now quite clear that the sphincter mechanism of the female urethra is more delicate and complicated than previously considered. When we regarded the urethra as having an internal and an external

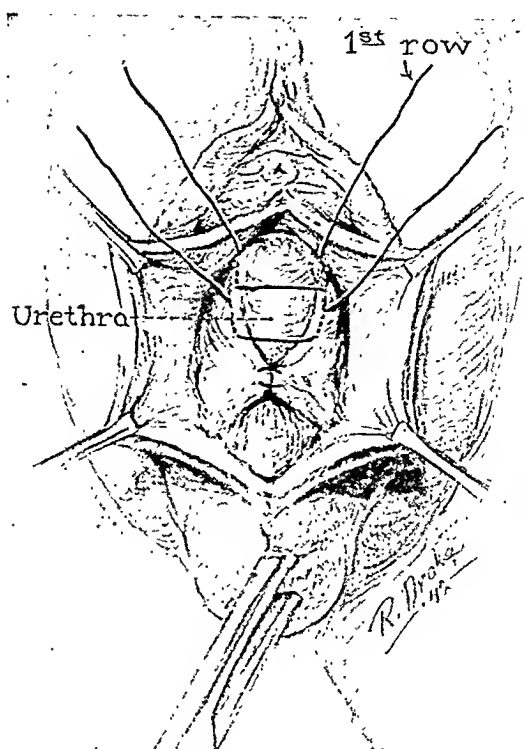


Fig. 6.—First row of mattress sutures plicating urethra.

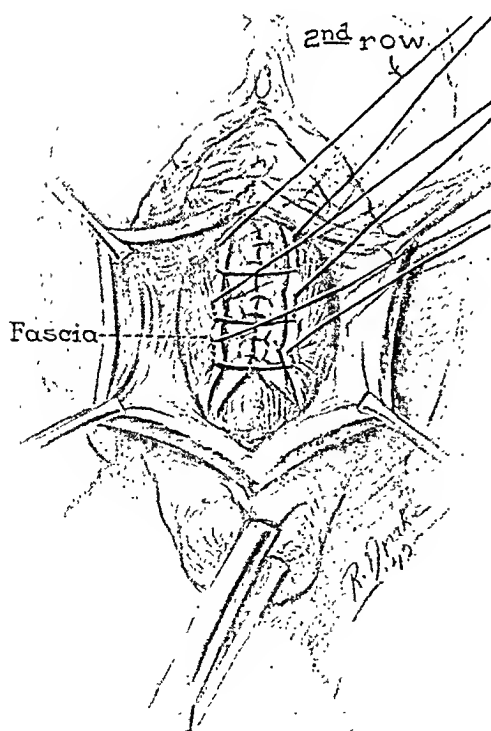


Fig. 7.

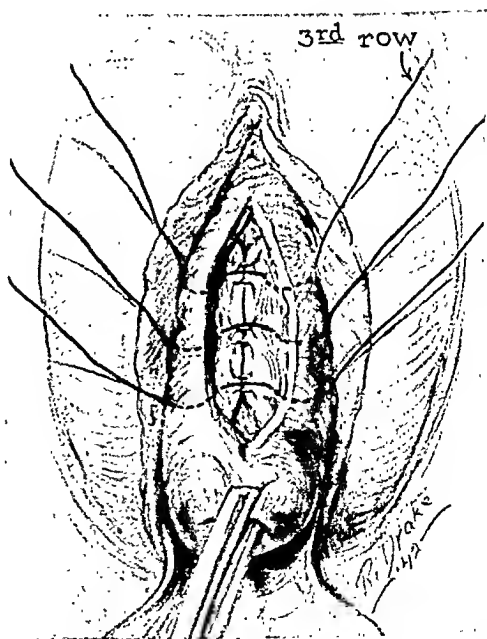


Fig. 8.

Fig. 7.—Further separation of urethra from pubic rami by second row of mattress sutures.

Fig. 8.—Reconstructing constrictor urethrae muscle and urogenital diaphragm beneath the urethra.

meatus (Fig. 5). The urethra is separated from the pubic rami on each side. This separation must be kept close to the bone to avoid a plexus of veins and branches of the inferior vesical artery, and must extend into the paravesical space. If this is gently done, fibrous adhesions between the urethra and pubic rami can be palpated and separated, restoring freedom of motion to the urethra. This freedom of motion must be maintained for complete relief of incontinence. This is accomplished by plicating the tissues under the urethra by three mattress sutures which hold the urethra from the pubic rami (Fig. 6). A second row of

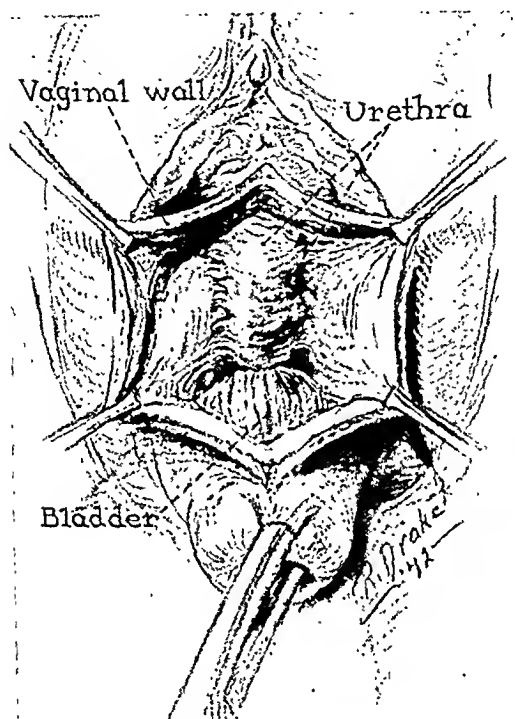


Fig. 5.—Anterior vaginal wall opened to 1.5 cm. of external urethral meatus.

mattress sutures picks up the edges of a fascia-like structure on the lateral surface of the urethra and these sutures when tied separate the urethra further from the pubic rami (Fig. 7). An additional mattress suture should be placed to plicate the inner portion of the urethra about the internal sphincter (Kelly stitch).

The restoration of the voluntary sphincter is now to be considered. The damaged portion of this muscle which remained attached to the vaginal wall is removed with the redundant portion of the vaginal wall which formed the urethrocele. The remaining intact sphincter fibers are replaced by three No. 1 chromic catgut sutures beginning at the highest point of the vestibule and extending down about 2 cm. These sutures are passed through the vaginal wall quite close to the pubic rami so as to be certain to catch the muscle fibers of the constrictor urethrae (voluntary) and inferior layer of fascia of the urogenital diaphragm. When these are tied the edges are replaced beneath the middle and inner portions of the urethra (Fig. 8). Kennedy⁷ uses silver wires instead of catgut. A male catheter is placed in the urethra for five to seven days or until the patient is out of bed, when she is advised to void as normally.

and he suggested a method of repair which has greatly improved the results.

It is hardly fair to state that this operation should be performed in every instance of incontinence, since records show that 60 to 75 per cent of patients received good results by other methods. The high percentage of failures when other methods were used should represent that group of patients who exhibit more damage to the sphincter mechanism than relaxation of the internal sphincter and proximal centimeter of the urethra. The author has used the method of repair suggested by Kennedy for 26 patients, all of whom were completely relieved of their incontinence.

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Discussion

DR. BAYARD CARTER, DURHAM, N. C.—My experience is limited to 8 cases. Operation was found necessary in 5 cases following a vaginal operation, in 1 following a cystocele and in 2 virgins who developed incontinence late in life. The difficulties we have had in the procedure are first to satisfy ourselves that we have been able to free the urethra and then to control the bleeding. In the old days we thought that 65 per cent of the cases would have good results with the ordinary Kelly procedure, but we do not feel so today and therefore incorporate the tension on the urethra in operations for true procidentia. We also use it in those cases of vaginal hysterectomy that develop incontinence of urine. It also makes an ideal conservative procedure in the occasional case of an aged virgin who develops an incontinence, either with or without an hypertrophied cervix.

DR. A. J. RONGY, NEW YORK, N. Y.—A word should be said about prevention in connection with urinary incontinence. Those of us who have had extensive obstetric experience have observed that the patients who have a thick, bony pubis and a low pubic arch, are more prone to develop incontinence in later life than those who have a high and normal pubic arch. Therefore such patients should not be allowed to have a prolonged second stage of labor because of the greater likelihood of damage to the anterior vaginal wall, including the neck of the bladder and the urethra.

Incontinence in virgins occasionally may be observed as a result of masturbation. I recollect an incident of this kind in a woman who admitted to excessive masturbation and frequently complained of urinary incontinence. She had no pathologic lesions to account for it.

DR. A. D. CAMPBELL, MONTREAL, CANADA.—The compressor urethrae muscle, lying between the layers of the so-called urogenital diaphragm, is in reality the deep perineal muscle but only a portion of this muscle (the anterior portion) is compressor in effect. One therefore cannot expect the compressor urethrae muscle to function properly when the free margin of the urogenital diaphragm is lacerated, for it is in

Results

The author has performed the Kennedy operation on 26 patients either as a primary procedure for various degrees of incontinence or in association with other surgical procedures for cystocele, prolapse, small fibroids, menometrorrhagia and lacerated perineum. The result in every instance was complete restoration of continence. Some patients contracted cystitis and urethritis of varying degrees, which induced some urinary urgency and frequency. These symptoms were all relieved through treatment in the Section on Urology before the patients were dismissed (Table I).

TABLE I. KENNEDY OPERATION

Complete Urinary Continence Restored in All 26 Patients in Whom the Procedure Was Carried Out by Author*

CASE	AGE, YEARS	SURGICAL DIAGNOSES			ASSOCIATED OPERATIONS†
		INCONTINENCE, GRADE‡	CYSTOCELE, GRADE‡	OTHER CONDITIONS	
1	49	1+	2		Vaginal hysterectomy
2	37	1	1		
3	40	2			
4	49	2	2	Prolapse, Grade 2	Vaginal hysterectomy
5	51	3			
6	44	2+			
7	52	2	2	Prolapse, Grade 1	Vaginal hysterectomy
8	40	3			
9	42	2	2	Prolapse, Grade 1	Vaginal hysterectomy
10	54	1+		Prolapse, Grade 4	Vaginal hysterectomy
11	42	1+		Fibroids	Vaginal hysterectomy
12	53	2	3	Prolapse, Grade 2	Vaginal hysterectomy
13	43	2	3		Vaginal hysterectomy
14	65	2			
15	48	1+	3	Prolapse, Grade 2	Vaginal hysterectomy
16	48	1+			
17	36	2+			
18	47	2+			
19	53	2	2+	Fibroids	Vaginal hysterectomy
20	67	1	2	Prolapse, Grade 2	Vaginal hysterectomy
21	44	3			
22	54	2+	3	Fibroids	Vaginal hysterectomy
23	51	1+		Menometrorrhagia	Vaginal hysterectomy
24	39	1+	1	Fibroids	Vaginal hysterectomy
25	51	1	1+		
26	49	2		Menometrorrhagia	Vaginal hysterectomy

*These results should be contrasted with other methods which showed 35 per cent failures.

†On a basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition.

‡Perineum was repaired wherever indicated.

Conclusions

The female urethra has an internal urethral and an external involuntary urethral sphincter. In addition there is a voluntary sphincter surrounding the middle third and extending posteriorly to cover the internal urethral sphincter partially. This sphincter is designated the sphincter urethrae membranaceae (Gray) and is the same as the external urethral sphincter in the male. Kennedy's investigation of this sphincter mechanism has served to clarify the real cause of incontinence

POSTERIOR VAGINAL ENTEROCELE*

Hernia of the Cul-de-sac of Douglas

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

(From the Carney Hospital)

POSTERIOR vaginal enterocele, or hernia of the cul-de-sac of Douglas, is a lesion which up to two decades ago had received but little attention in the literature. That it is fairly common is attested by the number of publications appearing during the last twenty years. In 1924, at the Cleveland meeting of this Association, I¹ presented a paper on this subject, reporting 4 personal cases. Since then my series has reached the number of 48, the results in which are reported below.

In 1909, Marion,² of Paris, brought this condition to the attention of the profession and described an abdominal method of obliterating the cul-de-sac of Douglas. In 1912, Moschcowitz³ described a similar procedure for the cure of prolapse of the rectum, this being equally applicable to hernias of the cul-de-sac of Douglas. In 1922, George Gray Ward⁴ discussed the subject of posterior vaginal enterocele before the American Medical Association and described a vaginal operation to overcome this condition.

Previous to the publication of these papers, posterior vaginal enteroceles were described, as they still frequently are, as high rectoceles. That this is fallacious may be proved by a careful dissection of the posterior vaginal segment, where there will be encountered a bulging of the cul-de-sac of Douglas above the rectum, the two being separated by a layer of adipose areolar tissue. The upper limit of the rectum may be demonstrated by introducing into it a well-lubricated gauze sponge at the end of a sponge stick or a ring forceps, when the mass bulging over the rectum will be found to be the cul-de-sac of Douglas. The contents of the mass may consist of large or small intestines, or omentum, or all three.

There are two etiologic factors responsible for these hernias: first, an abnormally deep cul-de-sac of Douglas, a congenital defect. With intra-abdominal pressure directed against the cul-de-sac, traction is made on the posterior lip of the cervix and on the anterior wall of the rectum, resulting in prolapse of the uterus, the rectum, and the anteriorly attached bladder. By this mechanism, a congenitally deep cul-de-sac of Douglas may be responsible, in most cases, for the so-called nulliparous prolapse. A second factor rests in the trauma of labor, consisting in the

*Read at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 10 to 12, 1942.

this fascia that the compressor urethrae muscle is actually fixed. Hence in reconstructing the muscular support of the urethra one must not overlook the remaining portion of the urogenital diaphragm.

I am of the impression that in a great proportion of cases previously operated upon for damaged birth canal the abdomen has been opened as part of the surgical procedure. The subsequent frequency in such cases is not due to the improper support of the urethra but to the adhesions of the bladder to gut, adnexa or omentum. The factor of extravescicular adhesions must always be considered.

DR. COUNSELLER (closing).—Dr. Carter stressed the question of bleeding during separation of the urethra and bladder from the pubic rami, and that is a very important point. If the inferior vesical artery is injured there will be considerable bleeding, and sometimes it cannot be avoided. I try to separate the bladder from the rami by keeping outside of the vascular plexus and adjacent to the bone. It may be impossible to control bleeding by ligature or suture. In such instances I simply put in a piece of iodoform gauze, and leave it in position for from three to five days.

It is also important that in the process of reconstruction the urethra be straightened. That is one of the primary purposes of the operation; another one is that of lengthening the urethra. Many times it is foreshortened, as beautifully illustrated in Dr. Kennedy's work.

I think what Dr. Campbell has said concerning scarring resulting from previous surgical treatment is particularly true if during abdominal hysterectomy an attempt was made to reconstruct the uteropubic fascia. If such procedures have not been done, much difficulty will not be encountered in reconstructing muscular control from the vaginal side, as in the Kennedy operation.

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TABLE II. DIAGNOSES

Posterior vaginal enterocele (Hernia of cul-de-sac of Douglas)	48
Additional Diagnoses	
Uterine procidentia	9
First-degree prolapse	1
Recurrent prolapse	3
Virginal prolapse	3
Prolapse of cervical stump	2
Hypertrophied cervix	2
Ulcer of cervix	1
Laceration of cervix	2
Cervical polyps	2
Cystocele	7
Rectocele	10
Vaginal ulcer	2
Hypertrophied suburethral fold	1
Complete laceration of perineum	1
Prolapse of rectum	1
Ventral hernia	2
Myomas of uterus	2
Diabetes	1
Cholelithiasis	1

TABLE III. PREVIOUS OPERATIONS FOR PROLAPSE IN THIS GROUP

OPERATIONS	PATIENTS
One previous	17
Two previous	4
Three previous	4
	25
25 of the 48 patients had had previous operations for prolapse.	

TABLE IV. OPERATIVE PROCEDURES

Ward vaginal operation	36
Moschcowitz operation	10
Total colpocleisis	1
Partial colpocleisis	1
	48
Additional Operative Procedures	
Vaginal hysterectomy	6
Interposition operation	6
Supravaginal hysterectomy	4
Fundectomy	1
Abdominal fixation of uterus	4
Incorporation of uterus in abdominal wall	1
Cervicopexy (abdominal)	4
Amputation of cervix	6
Trachelectomy (cervical stump)	1
Cauterization of cervix	1
Anterior colporrhaphy	1
Colpoperineorrhaphy	38
Bladder advancement	1
Resection of suburethral fold	1
Myorrhaphy of sphincter ani	1
Double salpingo-oophorectomy	4
Appendectomy	1
Cholecystectomy (2 weeks after plastic operation)	1
Incisional herniotomy	2
Hemorrhoidectomy	1

tearing or stretching of the thin rectovaginal fascia during parturition, and especially during operative deliveries; this results in the formation of a hernial sac, which keeps increasing in size as time goes on.

A hernia of the cul-de-sac may follow vaginal hysterectomy for the treatment of prolapse, if the cul-de-sac is not closed or obliterated. This may be prevented by approximating the uterosacral ligaments to each other in their entire length, as a part of the technique in all vaginal hysterectomies for the treatment of prolapse, since the united ligaments will act as a definite barrier against recurrence. Posterior vaginal hernia may also occur following a commonly accepted method of treating prolapse, namely amputation of the cervix, anterior colporrhaphy, perineorrhaphy, and fixation of the uterus to, or its incorporation in, the abdominal wall. Following this intervention a wide space is left posteriorly between the cervix and the rectum. In the course of ten to fifteen years, by my observation, a large hernia of the cul-de-sac of Douglas may develop. I have operated upon several women with such a recurrence.

There are three accepted methods of surgically treating these hernias: the abdominal method, recommended by Marion and Moseheowitz; the vaginal, proposed by George Gray Ward; and finally colpoeleisis, total or subtotal. The Ward vaginal operation is the ideal method, the abdominal being reserved for the very large and complicated hernias with adhesions, which make the vaginal dissection very tedious, if not hazardous. Colpoeleisis is employed in large hernias, where there exist contraindications to a laparotomy.

The vaginal intervention consists in freely dissecting the posterior vaginal segment to the cervix uteri or the vaginal vault, exposing the rectum and cul-de-sac hernia, picking the cul-de-sac, freeing it from all surrounding structures, opening it, reducing its contents, ligating its base, and resecting it. The uterosacral ligaments are then approximated in their entire length by interrupted sutures of fine silk or catgut, and the pelvic floor is repaired. The abdominal procedure relies upon the application of superimposed purse-string sutures, from below upward, in order to obliterate the cul-de-sac, using due care not to include the ureters in these sutures. If one is in doubt about the course of the ureters, catheters may be introduced into them as a preliminary step.

TABLE I. AGES

PATIENTS	
Between 35 and 40 years	5
Between 40 and 45 years	8
Between 45 and 50 years	4
Between 50 and 55 years	10
Between 55 and 60 years	8
Between 60 and 65 years	9
Between 65 and 70 years	3
Between 70 and 75 years	1
	48
The youngest patient was 36, and the oldest 73 years of age.	

wide space is left between the cervix and the rectum, through which a hernia may develop in the course of years.

4. A hernia of the cul-de-sac of Douglas should be differentiated from a high rectocele.

5. Lack of recognition of this condition leads to failures in operations on the posterior vaginal segment.

6. Vaginal and abdominal operations have been devised for the correction of this lesion.

7. The vaginal route is employed in most cases, while the abdominal route is reserved for very large hernias, and those complicated with adhesions.

8. Forty-eight cases of posterior vaginal enterocele are reported.

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Discussion

DR. A. D. CAMPBELL, MONTREAL, CANADA.—In looking over our statistics in the Gynecological Clinic of the Montreal General Hospital, over a five-year period, it was found that an enterocele was present in some 4.5 per cent of cases referred to us for repair of a damaged birth canal.

In the diagnosis, particularly in its smaller forms, an enterocele is often overlooked, particularly if it coexists with a rectocele. With the patient in the lithotomy position vaginal enterocele, or so-called high rectocele, becomes very much less apparent or may even seem to disappear. It is furthermore a problem to decide whether or not one is justified in repairing the smaller forms of this condition when the patient presents no symptoms which one can ascribe to the enterocele.

While it is true that with a sponge on a ring forceps, as described by Dr. Phaneuf, one can usually demonstrate the presence of an enterocele, there are cases in which one cannot be sure even by such a method. If there is any doubt as to the presence of an enterocele a small incision should be made through the vaginal vault as a preliminary to repair. Through this opening the cul-de-sac can be thoroughly explored and if a hernia exists its lower limit can be determined with accuracy. I have found that such a procedure is infinitely more informative and one less likely to damage the anterior wall of the rectum than any attempt to demonstrate or isolate the hernial sac by dissection.

In the repair of enterocele I am thoroughly in accord with Dr. Phaneuf that vaginal hysterectomy gives the most satisfactory surgical approach. By removal of the uterus all the structures concerned in this condition are more accessible to repair and can be more effectively employed to occlude the hernia. After the hernial sac is completely closed with a purse string suture and the excess peritoneal sac resected, the uterosacral ligament can be easily sutured into the pubocervical fascia and approximated to reduce the hiatus anterior to the rectum. In the repair of the posterior vaginal wall following the surgical resection of the vaginal hernia, the rectovaginal septum and the so-called urogenital diaphragm should be meticulously reconstructed so as to insure adequate support to the rectum and its ampulla.

Unfortunately, there are self-styled gynecologists who still think that procidentia or an enterocele or a damaged birth canal can be permanently corrected by affixing

TABLE V. ANESTHESIA

	PATIENTS
Spinal anesthesia	20
General anesthesia	28
	48

TABLE VI. MORTALITY

There was one death in 48 patients, a mortality of 2.08 per cent.
This patient, 73 years of age, was operated upon under spinal anesthesia, 100 mg. of novocain crystals having been used. The intervention consisted of an interposition operation, vaginal resection of the cul-de-sac of Douglas, approximation of the uterosacral ligaments and colpoperineorrhaphy.
The operation was performed on May 15, 1928. On May 16, 1928, she had a small pulmonary embolus, from which she recovered. On May 22, 1928, one week after operation, she had a second massive pulmonary embolus which took her life.

TABLE VII. RESULTS

There were three recurrences, Cases 2, 5, 19, 6.2 per cent
Case 2: Recurrence after Moschcowitz operation; six years after recurrence, total colpocleisis was performed, with a satisfactory result.
Case 5: Slight bulging of cul-de-sac after the vaginal operation.
Case 19: Slight bulging of cul-de-sac after the vaginal operation.

Results

The follow-up in this group of elderly patients, recruited from the New England States, has not been entirely satisfactory, as it has been difficult to bring them in for subsequent examination. All were examined at the time of their discharge from the hospital, and showed satisfactory primary results. They were re-examined within a year of operation, and 3 recurrences were discovered. Several of the oldest patients died of intercurrent disease. It must be borne in mind that in checking the results of vaginal hernias of any type, the more years are allowed to elapse, the higher will be the percentage of recurrences. Were we able to examine all of the patients alive at this time, our recurrences would probably be higher than 6 per cent. These operations were performed during a period of twenty years.

Summary and Conclusions

1. A deep cul-de-sac of Douglas may be congenital or be acquired as the result of parturition. In either case it plays an important role as a cause of uterine prolapse.
2. A hernia of the cul-de-sac may occur after a vaginal hysterectomy for prolapse if care has not been taken to approximate the uterosacral ligaments in their entire length at the time of operation.
3. A large hernia may develop following the combined method of operating for uterine prolapse, namely amputation of the cervix, anterior colporrhaphy, perineorrhaphy, and fixation of the uterus to, or its incorporation in, the anterior abdominal wall. Following this operation a

high, while the prolapsed area is posterior to the cervix and is due to enterocele. This is a true hernia. You can feel the small intestines and some of them are huge. I feel, with Dr. Phaneuf, that in such a condition after the uterus has been entirely removed the most satisfactory procedure is colpectomy.

DR. LEWIS F. SMEAD, TOLEDO, OHIO.—One of the most common failures in an operation for prolapse follows the Mayo type of operation in which the broad ligaments are brought together and fastened well forward under the symphysis. This leaves a weak place in the cul-de-sac behind the site of operation unless proper steps are taken to avoid it.

I have also had some trouble with shortening of the vagina in operating for posterior vaginal enterocele. I should like to ask Dr. Phaneuf what means he uses to prevent this shortening of the vaginal canal?

DR. VIRGIL S. COUNSELLER, ROCHESTER, MINN.—It was mentioned a moment ago that the Mayo type of hysterectomy often leaves a defect between the uterosacral ligaments, and that statement is definitely true. When this operation is used, the surgeon should try, with the tissues under tension, to identify the uterosacral ligaments and bring them together accurately, down as close as possible over the rectum, especially in obese patients where the uterosacral ligaments are infiltrated with fat and the rectal wall is covered with fat.

Shortening of the vagina in these cases is an extremely important factor, for if the vagina is not shortened recurrence is very likely. Fortunately, the majority of these enteroceles occur among older women who probably are not so much concerned about vaginal shortening as they are about complete cure. I am very careful to state to the patient and her husband prior to surgical treatment that the vagina perhaps will not be as deep as it was before.

DR. PHANEUF (closing).—When he finds a beginning enterocele, Dr. Campbell places a purse-string suture around the sac, approximates the uterosacral ligaments and repairs the pelvic floor. This works satisfactorily in the earlier cases, but in the advanced ones I believe it is better to dissect and remove the sac, approximate the uterosacral ligaments, and repair the pelvic floor.

I agree with Dr. Kennedy that the term "enterocele" is a misnomer, and that "hernia of the cul-de-sac of Douglas" is a better one; yet, the term enterocele is used throughout the literature. The clamp method of vaginal hysterectomy, as advocated by Dr. Kennedy, has taken care of the enterocele as well as the prolapse of the uterus in a number of my cases, and it took Dr. Kennedy ten years to convince me of the value of this method. I have learned by experience that in the healing which takes place after a vaginal hysterectomy by the clamp method, the cul-de-sac of Douglas is pulled up by the keystone which is formed between the broad ligaments and the vaginal vault. I have employed this method especially in elderly women, who are in poor physical condition, and have seen them obtain relief from their enteroceles and prolapses.

Replying to Dr. Vogt's question as to the treatment of an enterocele in a patient who has had a vaginal hysterectomy, I would say this always offers a problem. What I do in such cases is to open the posterior vaginal wall longitudinally to the vaginal vault, resect the sac, or obliterate it by means of superimposed purse-string sutures, approximate the uterosacral ligaments, unite the crura of the pubococcygeus muscles to narrow the general hiatus, and repair the pelvic floor. This usually gives relief. The patients are enjoined against doing any heavy lifting or straining. Should there be a recurrence at a later date when these women have become older, a colpocleisis would, undoubtedly, take care of the lesion.

Dr. Counsellor, like those of us who have operated on large enteroceles, finds that it is impossible not to shorten the vagina to some extent. This is something which the patient accepts if it is explained to her beforehand.

the uterus to the anterior abdominal wall. Such fixation in addition to being a futile operation, rather complicates subsequent vaginal herniotomy with vaginal hysterectomy as an incident in the procedure. The fixation pedicle in such cases is an object which has to be dealt with. Fortunately it can be ligated easily by passing a ligature around its stock. With the assistance of an ordinary bifid packing probe the knot can be slid upwards to its base and tied tightly so as to prevent oozing.

DR. JAMES W. KENNEDY, PHILADELPHIA, PA.—I have never liked the term "enterocele," as it suggests that the intestine has been a factor in its production which I do not believe is true. In several thousand vaginal hysterectomies where we have freely incised the posterior vaginal vault, entering the cul-de-sac of Douglas, I have never found the intestine in the cul-de-sac. The intestine does not prolapse until air has entered the pelvis.

If the fascia of the vaginal fornix and the uterosacral ligaments both are atrophied and lose their function, a true enterocele will not be found, but if the fascia of the vaginal fornix alone gives way and the uterosacral ligaments are intact, then the true enterocele makes its appearance and gives the posterior vaginal wall the dumbbell appearance.

In nearly all the patients I have seen, there has been a marked degree of prolapse of the uterus with a marked cystocele and so I perform vaginal hysterectomy by the clamp method. The ideal procedure in these cases of late prolapse where enterocele and rectocele become a common lesion from descent of the uterus, is first to perform a vaginal hysterectomy by the clamp method combined with a radical cystocele operation, and later to do a high posterior repair of the vaginal wall. The retraction of the vaginal fornix incidental to the clamp method of vaginal hysterectomy and the extensive cystocele operation, followed later by a high repair of the posterior vaginal wall, has always given perfect relief of the miserable condition.

Substantial suture material must be used and we employ silkworm-gut in all our repairs.

DR. WILLIAM H. VOGT, St. Louis, Mo.—I am not very often able to make the diagnosis of enterocele before the operation is started. The diagnostic method that Dr. Phaneuf has brought out, namely by putting a sponge into the rectum, applies after the operative field is exposed. Even then it may be difficult and not until you have dissected the tissues thoroughly do you recognize that you are dealing with an enterocele. In some cases even we have believed that we had done a nice repair of a rectocele but the patient has returned with a bulging over the perineum bigger than it was before the operation. In such cases we have failed to recognize the condition.

I was glad to hear Dr. Phaneuf admit that if you watch these patients long enough you will see a number of recurrences, even though you have done the enterocele operation carefully, because after a number of years some patients, who are obliged to do hard work, or who inadvertently lift heavy objects, have a recurrent enterocele or a prolapse after the original operation.

I would like to ask Dr. Phaneuf how he would handle a prolapse of the posterior vaginal wall, which proved to be an enterocele, in a patient in whom a vaginal hysterectomy had been done and who is still in the years of sexual activity, not much over 40 or 45 years old? Should another attempt be made to dissect out the hernial sac and close it in the same manner as in the original operation?

DR. BENDER Z. CASHMAN, PITTSBURGH, PA.—Unrecognized enterocele, is, I believe, the most common cause of recurrence after prolapse of the uterus. The new lesion, however, is not always an actual recurrence of the prolapse of the uterus itself. The cervix or vault of the vagina after these operations may be held rather

selves in failure of ovulation and resulting corpus luteum formation, which in turn would eliminate progesterone as a modifying influence on the gonadotropic secretion of the pituitary. At the same time the ovary might respond to the follicle-stimulating portion of the pituitary in which event one would expect bleeding from estrogenic endometrium when alterations in estrogenic levels occur. As these alterations become less pronounced, bleeding ceases. With the ovarian influence removed the cyclic function, qualitatively and quantitatively, of the pituitary is lost and the gonadotropic function is maintained at a higher and constant level.

Thyroid.—The behavior of the thyroid gland varies. In all probability there is increased thyrotropic influence from the less inhibited pituitary. It is noteworthy that symptoms of hyperthyroidism are often encountered at this time. However hypothyroidism may be noted, though not so frequently.

Pituitary.—Many functions have been ascribed to the anterior pituitary and many hormones have been thought to come therefrom. The pituitary is relatively a small organ and contains only several types of cells. It is situated in the middle of the skull where a slight increase in size or deviation from the normal would readily be interpreted in terms of headache, visual disturbances, x-ray findings, physical alterations, blood hormone changes, or other recognizable symptoms. How much simpler the problem would be if it could be shown that the anterior pituitary put out a "universal" hormone which served all the demands of growth, thyrotropic, gonadotropic, lactation, and other pituitary functions. There is a distinct probability that investigators have been "chipping off" portions of a hormone and carrying it in the direction of their research and interest. The alterations of the pituitary by other hormones, by depressing its function and probably by dilution, is more easily understood. It is our belief that histologically the pituitary is fairly constant.

Most of our attention in the past has been directed to the pituitary-ovarian relationship. Lately the role of the endometrium has been appreciated, and now it seems orderly and proper that the adrenal must be considered as a more integral part of sex endocrinology.

Adrenals.—The adrenal steroids have a similar chemical structure to the estrogens and it would seem that they might substitute for the lowered estrogens in an effort to depress and stabilize its relatively uninhibited pituitary. It also is likely that the medulla of the adrenal also is effected by this stimulation which would result in an increase of epinephrine. This could explain the well-known instability of the vasomotor systems in climacteric women, an instability which certainly is the chief indication for remedial measures.

Estrogenic ovarian failure, more severe in degree than that which occurs in many instances of intercurrent amenorrhea during the repro-

THE INVOLUTIONAL PHASE OF THE MENSTRUAL CYCLE (CLIMACTERIC)*†

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THE term "menopause" strictly applies only to the cessation of the menstrual periods, while the term "climacteric" refers to the period of reproductive regression and is to be preferred. Often this epoch is considered as a disease or syndrome, the process of living and associated influences not being considered. Under any circumstance and in either sex the five-year period (from 40 to 45 or 45 to 50) is a critical and exacting one. In the married female either the presence or lack of a family may be equally disturbing. The realization that the last chance of reproducing has passed, with the woman who desires a child, or the fear of pregnancy at this late date in a woman who has reared a family may disturb mental tranquillity. The childless woman who has not made adequate adjustment or the devoted mother who, with uncompensated grief, sees and feels her children breaking home ties, makes demands on natural reciprocity. The business of educating a family, seeing that it is favorably presented, and assuring it some degree of security is most exacting. The husband is a remarkable factor. The successes and failures over a period of years, the multiform problems that he has brought home, and, equally important, has not brought home, the precarious endeavor, at a time when his mental and physical agility often are incorrectly and prejudicially estimated, in trying for the last deal that will give economic independence all add doubt and worry to a varying and chaotic mind. These and many other reflecting factors make one realize that the climacteric is not a disease unless one considers living and the ageing process a disease. It also gives an insight into the probable inadvisability of routine substitutional therapy, given in an attempt to push back and withhold the natural gradual sequences associated with the climacteric.

Hormonology of the Climacteric

Ovary.—From many and varied observations we realize that there is a definite functional limit to the ovary. In the beginning increased refractivity to the pituitary gonadotropes which would manifest them-

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Group A comprised 4 women whose ages ranged from 42 to 49 years and whose elapsed time since menstruation was from five to twelve months. The excretion values in these women averaged 77 I.U. or 64 per cent increase.

Group B comprised 5 women whose ages ranged from 48 to 57 and whose elapsed time since menstruation was from two to five years. The excretion values averaged 93 I.U. or almost 100 per cent increase over upper limit of normal.

Group C comprised 3 women whose ages ranged from 62 to 74 years and whose elapsed time since menstruation was from fourteen to twenty-six years. The excretion values averaged 39 I.U., which was within normal range.

An analysis of the data suggests the theory of ovario-adrenal reciprocities, which are influenced chiefly by way of the pituitary. During early life and until adolescence is well advanced, the adrenopituitary interchange is dominant in steroid metabolism. When primary or adolescent hypoovarianism occurs and is of sufficiently severe grade to result in failure of sexual maturation, this axis retains its dominant position even during adult years. Under these circumstances, the level of adrenal function remains about that characteristic of late preadolescence. Normally, however, with the advent of adolescence and the beginning of full ovarian function, the ovaripituitary interchange is superimposed upon the primordial adrenopituitary one. The result is a harmonious arrangement wherein the pituitary becomes conditioned to working with both adrenals and ovaries and to being influenced, as regards its functions by the regulatory effects of the intrinsic steroids of both the ovaries and the adrenals. During the reproductive period, the ovary and pituitary come to dominate the endocrine system. When, however, ovarian failure occurs from pathologic or physiologic causes, the pituitary, accustomed to being balanced in function by both the adrenal and ovarian steroids, is released in part from its inhibitions and, thereby, becomes hyperactive, then the adrenal cortex is stimulated to secrete greater quantities of steroids. The now dominant adrenopituitary interchange is stronger because of its previous conditioning by the ovary and pituitary. Eventually, however, stabilization occurs from the inhibiting effects of the increased amounts of adrenal steroids upon the function of the pituitary. The result is that during the late stages of sexual ageing and during somatic senescence, the adrenopituitary axis becomes stabilized and steroid output reaches normal levels.

Complications of the Climacteric

If there is any inherent weakness in the individual it is likely to become manifest at the climacteric. There are certain complications that are more often found and should be anticipated.

Irregular and Postmenopausal Bleeding.—The only natural and normal course of menstruation at this time of life is cessation. This may

ductive period, occurs physiologically during the sexual ageing of woman or may be induced by radium or roentgenologic therapy. Complete ovarian deficiency occurs in bilaterally oophorectomized women. In all of these instances, the causes of the failure may be reduced to a simple common denominator, intrinsic ovarian damage, resulting from senility, radium, roentgen ray, or surgery. Patients with this type of intrinsic ovarian failure afford an excellent opportunity for the investigation of possible alterations in the androgenic functions of the adrenals secondary to ovarian deficiency or deprivation. If the findings reported upon patients with amenorrhea were interpreted correctly, studies of 17-ketosteroids excretion during the climacteric and after artificial menopause should show similar, if not more marked, elevations to those during amenorrhea.

Forty-one women during the climacteric or after artificial menopause were studied. They were grouped according to the cause and degree of ovarian failure incidental to this state. A total of 528 determinations was made, an average of 12.9 per patient.

In Group I, there were 12 women between the ages of 35 and 51 years, none of whom had ceased to menstruate, who had symptoms that are generally recognized as due to spontaneous estrogenic deficiency associated with the menopause. The average daily titer of these patients was 36 to 121 I.U. with a mean average for the group of 69 I.U., which represents an increase of 50 per cent over the normal. It is interesting to note that the group from 35 to 44 years had a mean average of 88 I.U., while the mean average of the group from 46 to 51 years was 43 I.U. which places emphasis on age rather than the actual cessation of menses in the compensatory adrenal activity.

In Group II, there are 5 women who had had radium or x-ray therapy from three months to three years previously. The average daily titer was 49 I.U. which is consistent with our ideas of ovarian impairment following the use of such agents. It is difficult to judge with certainty when one can expect absolute hypoovarianism from these procedures.

In Group III, there were 12 women who had complete ovarian failure from previous bilateral oophorectomies. In order to get more exact information, they were further divided into three groups according to the time of operation.

Group A comprised 5 women whose operations had been done nine to twenty-four days before the time of the collection of the last twenty-four-hour specimen for study. Their daily average of excretion was 25 I.U.

Group B comprised 5 patients whose operations had been done seven months to eight years previously, and in these patients the daily titers were increased to an average of 74 I.U.

Group C comprised 2 patients whose operations had been done sixteen years previously, and both of these patients showed normal excretion value of 40.

In Group IV, there were 12 women who had had normal physiologic menopauses. They also are divided into three groups according to the length of time since the cessation of menstruation.

description. Sweating, dizziness, headache, and sleeplessness are other symptoms. Uncertainty, a sense of impending tragedy and various inchoate states may result. These can and should be anticipated. In fact anticipation, explanation, and preparation are the best therapeutic agents.

Therapy

First one should ascertain to his own satisfaction that he is actually dealing with symptoms of the climacteric. The keystone in therapy is making the woman acquainted with physiology of the process, an adequate stock taking, an explanation of what to expect, assurance of the temporary nature of the state, a discussion with the husband and adult members of the family, and a sincere assurance that you as a doctor and counsellor will be at hand for any service.

If our treatise is predicated on a sound basis, the first therapeutic agent called for should be psychotherapy. Simplified this means that we should take the time and trouble to make a definite diagnosis, rule out complicating factors, such as malignancy, and that we can sit down with our patient and devote such time to the discussion of her ailments as is necessary to put her mind at ease. When this is not enough we should resort to simple sedation and, in definite instances and under supervision, to organotherapy. In this event the estrogens are the logical choice. They should be kept at such a low level as not to cause endometrial stimulation with resulting uterine bleeding. Our preference is to give them by mouth and in a dose lower than usually prescribed. Emmenin 480 to 960 day oral units, or some other preparation in similar small doses may be given. Occasionally hypodermic medication may be required but here again the dose should be held at its minimum. Recently diethylstilbestrol has been accepted for inclusion in "New and Nonofficial Remedies" and the dosage recommended is 0.5 to 1.0 mg. It is our feeling that $\frac{1}{10}$ to $\frac{1}{2}$ this amount would give this necessary relief and would not be likely to cause uterine bleeding or influence the as yet unknown possibility of carcinogenesis. It is a potent therapeutic agent and its value is proved. It must be regarded as a potent agent.

Progesterone, in our hands, has been of little value in treating symptoms of the menopause.

If the generally accepted concept of the climacteric is true and if our quantitations of the 17-ketosteroids can be accepted, there is no place for androgen therapy at, or following, the menopause unless we wish to hasten or aggravate the process. Androgen therapy is predicated on its "estrogen negating." Such a state is flagrantly evident at this time. As yet no syndrome in the female has been ascribed, critically or otherwise, to a hypoandrogenic state. If this is true one should doubt the validity of its use in female endocrinotherapy.

be a gradual diminution of the amount at each period or a lengthening of the interval. In any event the trend should be toward stoppage. The basis for this was given in the discussion of the hormonology. Any departure from this course during or after the menopause must be investigated and due account given. The occurrence at this time of hyperestrogenic endometrial bleeding has been noted and the association of this with corporal carcinoma has been suggested. Curettement of the uterus and careful study is obligatory. Empiric endocrine and x-ray therapy is condemned and the removal of endometrial tissue for biopsy examination by the "punch" method is inadequate. In any event satisfactory diagnosis must be made for this type of bleeding.

In one year 1,089 women in North Carolina died of cancer. Of this number, 324 died of cancer of the uterus. In that year 15,732 females died in the State. This means that one woman out of every 15 died of cancer and that one out of every 48 died of cancer of the uterus. To state it another way, 196 more women in this State died from cancer of the uterus than from appendicitis. Seventy per cent were diagnosed only on admission to the Hospital.

Thyrototoxicosis.—This possibility must be investigated and eliminated before the blanket indictment of the "menopause syndrome" is made.

Psychoses.—One should remember that the business of living by this time (40 to 50 years of age) is beginning to make inroads and the exigencies of life are likely to become manifest. It is a recognized fact that women under certain circumstances and conditions, at this time may become melancholic. A noteworthy instance is the rural female, whose endocrinology, in all probability, is no different from that of her urban sister. One should dissociate the recognized and proved symptoms of the climacteric, such as vasomotor disturbances, from the psychic aberrations that are not peculiar to the sex.

The psychiatrists have cautioned that estrogenic therapy should not be exhibited unless one is treating definite symptoms such as "hot flushes." This in spite of the enthusiastic reports of the specific benefits of the estrogen in involutional melancholia. It is impossible to separate specific from suggestive therapy under these circumstances and as a matter of fact psychotherapy should be the first agent in treating a psychosis. There is a distinct possibility that organotherapy may be a distinct menace. Overzealous, indiscriminate or routine therapy, may result in bizarre symptoms and actual harm.

Vasomotor Symptoms.—In all probability vasomotor phenomena are the most consistent symptoms associated with the climacteric. As a matter of fact the frequency and severity of these symptoms are used as criteria for diagnosis and treatment. Since these are the most frequent and disturbing symptoms, therapy should be directed toward relief. The most frequent complaint is "hot flushes" or "flashes." This symptom is so consistent and well understood that it requires no

The fundamental cause of the menopause is the cessation of ovarian activity. Because of the reciprocal, "seesaw" relationship between the ovary and the anterior hypophysis, cessation of estrogenic function means a relative increase of the pituitary gonadotropic function. By the administration of estrogens we can fill the estrogen deficiency, and let the patient down gently through this transition phase. Dr. Ross has properly emphasized, however, that the mechanism of this epoch may not be quite so simple as this, and that other endocrine glands, especially the adrenal cortex, may play an important role. The concept which he has presented of a phase of adrenal dominance following that of the ovary is a plausible and attractive one, and it may well prove correct.

While everyone now accepts the efficacy of estrogenic therapy for genuinely menopausal symptoms, we should remember that only a comparatively small proportion of menopausal women need any organotherapy at all. Many need only simple instruction and reassurance. Up to about twenty years ago gynecologists were likely to be either enthusiastic ductless gland faddists or hard-boiled skeptics. Looking back at this phase, the skeptics were correct, for the preparations then available we now know were practically devoid of hormonal virtue. Now, however, we have at our disposal preparations of unquestioned estrogenic efficacy, and our results have improved correspondingly.

The introduction of the nonhormonal estrogenic substances, represented especially by diethylstilbestrol, has been a godsend to menopausal women, because of their efficacy by oral administration and their inexpensiveness. Certainly the incidence of unpleasant side-effects, in the small doses now advocated, is far less than the figures of 80 to 90 per cent formerly given by some authors.

There should be no such thing as a routine method of stilbestrol therapy, and I believe it to be bad practice to start a woman off on this drug and have her continue its use indefinitely, even though the dose is small. The drug should be given intermittently, and only when indicated by definite symptoms. Excessive or prolonged dosage carries with it the risk of producing bleeding, which may be a disturbing factor, especially in women who had ceased menstruating a year or two previously, because it must lead to the suspicion of adenocarcinoma. I have recently had sent to me sections of curettings following just this sequence of events. They showed a proliferative type of hyperplasia which had been diagnosed as adenocarcinoma by a competent pathologist. I believed the lesion to be entirely benign and advised repetition of the curettage a few weeks later, the stilbestrol having of course been discontinued. An amazing retrogression was revealed at the second curettage, the endometrium then being of the characteristic senile atrophic type.

DR. GEORGE F. PENDLETON, KANSAS CITY, Mo.—What is your conception of why an ovary stops its activity at this time of life?

DR. NOVAK.—I think that can be about the same as to say why is a man's life three score years and ten. The ovary has a more or less foreordained life span and at the end of that time it comes to the end of its span of existence. This limited span of life is something innate in the mechanism and structure of the ovary.

DR. E. C. HAMBLIN, DURHAM, N. C.—I should like to emphasize the need for careful diagnostic studies when the problems of climacteric women are under consideration. The various symptoms of women of climacteric age cannot be related etiologically to the climacteric processes by recourse to chronologic considerations alone. In addition to a careful organic inventory designed to rule out intercurrent disease, the psychiatrist is often highly helpful in the evaluation of function at the psychic level. Many of the symptoms of climacteric women result more assuredly from psychic errors than from hormonal ones. Various involutional states, such as involutional melancholia, are not improved specifically by treatment with estro-

The complications of the climacteric should and must receive primary consideration in therapy. Only after they, especially the possibility of cancer, have been evaluated should one outline definite treatment for the climacteric.

It is well to remember that muscle tone and sex steroid levels, especially the estrogens, have a relationship. There is a definite loss of tone and diminution in size of the organs, muscles, mucosa-supporting structure of the pelvis. Any pelvic repair or advice regarding repair should take account of this fact.

Summary

1. The term "climacteric," describing the period of normal reproductive regression, is preferable to the term "menopause," which simply designates the final menstrual period.

2. This epoch should not be considered a disease, unless the process of ageing and living is so considered. Neither should it be considered as entirely dependent and definite with ovarian failures. Many other factors, occult and manifest, influence the severity of the process.

3. The hormonology of the climacteric is now generally better understood. Refractivity of the ovary to pituitary stimulation, failure of ovulation, gradual lag in the response to follicle stimulation with receding waves of estrogenic output, a temporarily uninhibited pituitary with varying adrenal and thyroid stimulation is a brief summation.

4. The complications of the climacteric should be investigated before therapy is instituted. These are irregular bleeding, vasomotor phenomena, abnormal psychic states, thyroid disorders, pelvic relaxation, and systemic breakdowns.

5. The therapy should include practical and orthodox psychotherapy, explanation and correction of irregular bleeding, systemic treatment, necessary repair work, mild sedation and organotherapy.

6. Progesterone is of little value. Thyroid may be indicated. There is no indication for the androgens. Estrogen therapy has definite value. Preferably it is given by mouth in smaller doses than those usually prescribed. The daily dose of diethylstilbestrol, if used, should not exceed 1 mg. a day. Smaller doses are preferred and usually suffice.

Appreciation is expressed to Dr. E. C. Hamblen for the use of material that gives these observations a factual basis.

Discussion

DR. EMIL NOVAK, BALTIMORE, MD.—There is still a widespread tendency among practitioners, almost as much as among the laity, to ascribe to the menopause almost any nervous manifestation appearing in women over 40. Such symptoms are far more likely to be due to other causes, such as domestic or economic worries. To tell such women that they are "beginning to change" is the easy but the wrong way out, especially if it means resort to organotherapy, as too often it does.

factitial changes are present, only edema and diffuse reddening may be seen. The condition is encountered most frequently in a later stage than this, when bleeding from the rectum causes the patient to come for examination. By this time telangiectasis usually is present and is the cause of the bleeding. Often the reparative process of telangiectasis is noted early. The little, new blood vessels situated superficially in the rectal mucosa are broken by the slightest trauma. The anterior wall of the rectum, in its middle third, usually is reddened and studded with numerous capillaries. Merely swabbing this area lightly with a cotton applicator is sufficient to produce diffuse oozing of blood. Often it is necessary to defer examination on this account. In most cases the inflammation loses its intensity gradually but the process of healing is slow. After healing, the inflamed tissue is replaced by mucous membrane which possesses a yellow tint owing to deposit of scar tissue. Telangiectasis persists and, because of the vulnerability of these capillaries, bleeding from the rectum may occur from time to time over long periods. Indeed, in some cases in which the patients have been followed for years, this bleeding has continued to occur and it may persist as the only symptom of the condition. This presents an unfortunate problem. Many of the patients become "rectum conscious" and are never relieved of concern. These patients should present themselves for examination regularly.

The factitial ulcer is oval or irregularly circular and usually involves all layers of the rectal wall. Mobility of the diseased portion may be limited because of adherence to structures adjacent to it. The size of the ulcer averages from 1 to 3 cm. in diameter, the margins are smooth and regular in outline and the base, which is depressed, is covered with a silver gray or yellowish membrane, which is rough, slightly piled up and very tenacious and tough. The base of the untreated ulcer is covered with an ugly, slimy, greenish gray slough. Telangiectasis is always present in the mucosa surrounding the ulcer and with it various degrees of proctitis extend outward from the margin of the ulcer. Usually the ulcer is single. Occasionally there may be more than one. The inflammation and ulceration have a tendency to heal and, if the carcinoma does not terminate the patient's life, the factitial lesion usually will undergo resolution.

Symptoms

We have data on 88 cases in which significant symptoms led to proctoscopic examination and a diagnosis of factitial changes in the rectum following radiation therapy. These symptoms in order of frequency were most commonly bleeding from the rectum, frequent desire to go to stool, liquid stools, pain in the rectum, mucous discharges, and constipation. Other complaints that were made less frequently were of abdominal cramps, decrease in the size of the stool, and tenesmus.

gens; indeed some are aggravated. A good principle to follow is: treat no climacteric woman with estrogens who does not count hot and cold flushes among her symptoms, although these vasomotor vagaries are by no means invariably pathognomonic of the climacteric.

DR. BAYARD CARTER, DURHAM, N. C.—There is one condition which has not been mentioned in which I think estrogenic therapy is highly valuable, and that is in women who have a prolapse. It has a particular advantage in the senile group of women who have put off operative procedures. I am convinced that preoperative estrogenic therapy makes the closure much more scientific and avoids surgery on their vaginal walls.

FACTITIAL PROCTITIS*

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MALIGNANT disease of the pelvic viscera of women, when sufficiently advanced, precludes the possibility of surgical operation; then treatment by radium or roentgen rays is required. Such treatment aims to destroy only the malignant tissue but sometimes the structure of other tissues exposed to the irradiation undergoes certain alterations. "Factitial proctitis"† is a term used to designate such a condition that is sometimes discovered in the wall of the rectum. Usually this lesion appears on the anterior wall of the rectum but in severe cases all walls may be involved. It varies in severity from mild inflammation of the rectal mucosa to complete dissolution of a portion of the rectovaginal septum. This factitial lesion may not be avoided in all cases. It does not indicate that poor technic has been employed. If treatment by irradiation will destroy or impede the malignant process, the possibility of proctitis occurring should not, and does not, interdict such treatment.

Pathology and Diagnosis

Following irradiation of some pelvic structures, usually the uterine cervix, induration and deformity develop in the tissues adjacent to the rectum. Palpation of the anterior wall of the rectum therefore may not give an accurate picture of the situation. If there is an ulcer it may be felt as an indurated crater, but often irregular thickening in the structures adjacent to the rectum will give the same impression, even when the wall of the bowel is intact. Factitial proctitis, not associated with formation of ulcer, cannot be detected by palpation. It is necessary to view the rectum by means of the proctoscope in order to detect the true nature of the condition of the rectal mucosa. When early

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†The term "factitial" is defined in Dorland's *American Illustrated Medical Dictionary*, page 535, "produced by artificial means; unintentionally produced."

ing 9 cm. In 6 cases the faetitial involvement was diffuse and in the remainder it was circumscribed and located on the anterior wall of the rectum.

The faetitial uleers were found in the same area as the proctitis. The uleers varied from 0.5 cm. in diameter to 6 by 4 cm.

In 25 cases reduction in the size of the rectal lumen was noted. This deformity involved the same portion of the rectum as the inflammatory and ulcerative disease already described. The lumen of the rectum was not reduced to less than 2 cm. in any case.

The site of rectovaginal fistulas was 5 to 6 cm. above the dentate margin. Two fistulas had occurred after radiation treatment of carcinoma of the cervix. In one other case a fistula developed after treatment of a primary carcinoma of the vagina.

Results

Thirty-two patients are known to have died of malignaney; 26 could not be followed and 30 were followed from eight months to thirteen years. Of these 30 patients who were followed, 25 noted marked improvement in the rectal symptoms after the acute stage of the condition subsided. Most of them experienced occasional bleeding from the rectum, some a tendency to constipation and one stated that the stool was reduced in size. Four patients stated that constipation was a considerable problem and one patient alive at the time of writing of this paper, four years after treatment had a rectovaginal fistula.

Illustrative Cases

CASE 1.—A woman, aged 50 years, had had one pregnancy. In January, 1940, a diagnosis of carcinoma of the uterine cervix had been made and treatment with radium and roentgen rays had been administered. In the course of the latter treatment she had experienced diarrhea, having as many as twenty-five discharges from the rectum each day. Following this there had been a tendency to constipation. In April she had been told that she had an ulcer in the rectum. She had experienced pain in the rectum but had noticed no bleeding.

In May, proctoscopic examination was performed. The lower half of the rectum was involved by an acute inflammatory process and the anterior wall, at the junction of the middle and lower thirds, was broken down into an ulcer 3 cm. in diameter. Severe pain was produced by the examination.

In October, proctoscopic examination did not cause pain. The condition of the rectum appeared much improved. At this time, the ulcer was about 2 cm. in diameter and much of the inflammatory change had disappeared.

In July, 1941, the patient related that occasionally some bright blood passed from the rectum, but there was no pain on defecation. On proctoscopic examination at this time, the area on the anterior wall, that had been the ulcer, was still of the same size but most of it had healed over. Telangiectasis was present. There was still, and probably always will be, general oozing of blood from the rectal walls.

CASE 2.—A woman, aged 46 years, had been pregnant twice. Diagnosis of squamous cell epithelioma, Grade 4, Stage 2+, of the uterine cervix

The average time that elapsed between the initial course of treatment and the appearance of symptoms was ten months. Ten patients complained of various rectal symptoms that commenced immediately after treatment, and three patients noted the first symptom, bleeding from the rectum, thirty-eight, forty and forty-eight months, respectively, after the initial treatment.

Results of Examination

In 61 cases we know the type of pathologic lesion and the grade* of involvement for which treatment was administered. Fifty-one lesions were squamous cell epitheliomas of the uterine cervix; 3 were adenocarcinomas of the uterine cervix; 1 was a tumor containing both squamous carcinoma and adenocarcinoma; 1 was a primary carcinoma of the vagina; 1 was a papillary carcinoma of the ovary; and 4 were inoperable, extensive carcinomas of the uterine body. Seventeen tumors were found to be of Stage 4, 32 of Stage 3, and 12 of Stage 2. The grade of malignancy of the lesion and the amount of radiation given in each of these 61 cases is known. However, these data will not be presented because no useful correlation of them with the occurrence of factitial proctitis was ascertained.

The remaining 27 patients were among those who came to us after treatment elsewhere and in whose cases we were unable to verify the pathologic diagnosis. Of these, in 12 cases the neoplasms were judged clinically to be carcinomas of the uterine cervix of modified Stage 4; 6, of modified Stage 3; and 2, of modified Stage 2. In 7 cases it was not possible to learn why the patient had received irradiation.

Sixty of the 88 patients were examined through the proctoscope but once, for the reason either that they did not return to the clinic or that at a later visit, symptoms did not justify the examination. The remaining 28 patients were examined through the proctoscope two or more times over periods of two months to thirteen years. Twenty patients were examined twice, 4 patients were examined three times and 1 patient each was examined four, five, six, and seven times. The diagnoses made in the 88 cases are given in Table I.

TABLE I. DIAGNOSES MADE IN EIGHTY-EIGHT CASES

DIAGNOSIS	CASES
Factitial proctitis without stricture	39
Factitial ulceration without stricture	23
Rectovaginal fistula without stricture	1
Factitial proctitis with stricture	15
Factitial ulcer with stricture	8
Rectovaginal fistula with stricture	2

In 16 of the total of 88 cases, biopsy was performed and the diagnosis was inflammatory tissue in all but one, a case of primary carcinoma of the vagina.

The location of the factitial proctitis varied from just above to 20 cm. above the dentate margin, the average distance above this point be-

*The classification of lesions is that of the League of Nations, Health Organization, Cancer Commission: report submitted by the Radiological Sub-Commission. Geneva, *League of Nations Publications*, 1933.

tissues not involved in the malignant process. However, should he be so cautious that he always avoids such incidental damage he may treat the neoplasm inadequately. Considering the very small percentage of patients treated with irradiation whose normal tissues sustain significant damage, and the gradual improvement in results following such treatment, it seems that factitial proctitis and ulceration, and the occasional rectovaginal fistula, must be accepted as risks that the patient should assume when such treatment is undertaken.

Discussion

DR. DAVID LUDWIG, PITTSBURGH, PA. (By invitation).—Our experience in postradium proctitis is limited to five in a series of 334 patients suffering from carcinoma of the cervix. Our observation covers a twenty-year period, although the 5 patients suffering from proctitis were treated in the last eight years. During this time 150 patients have been treated for carcinoma of the cervix. The average amount of radium treatment was 4,800 mg. hours, while the smallest dose given was 2,300 mg. hours. Divided doses were utilized in all patients receiving more than 6,000 mg. hours. In this series one patient developed ulceration without stricture, one had a rectovaginal fistula with stricture, and two proctitis without stricture.

One patient, a woman of 53 with a history of one pregnancy, will serve as an example. When first examined in November, 1935, there was an area of carcinoma on the right posterior vaginal wall about 4 cm. from the mucocutaneous junction. The past history showed, however, that in June, 1930, the patient had received 2,450 mg. hours of radium for adenocarcinoma of the fundus of the uterus. In October of that year complete hysterectomy was performed and the laboratory reported adenocarcinoma of the fundus of the uterus and chronic salpingitis. The patient reported also that she had been treated with small doses of radium a few months prior to our examination.

The carcinoma was now excised and the tissue reported secondary carcinoma of the vagina. Radium was given as follows: 8 radium seeds, 4 needles of 12.5 mg. each, and a capsule of 50 mg., totaling 2,060 mg. hours.

In April, 1936, a slough of the vaginal area with induration was observed. Proctoscopic examination showed that the anterior rectal wall was much reddened and slightly edematous with bleeding upon manipulation. Six weeks later there was a small area of ulceration although with treatment the patient was more comfortable than when the proctitis was first observed. In July, 1937, proctoscopic examination showed that the rectal mucosa was much improved. There was a small scar with slight bleeding upon manipulation. The patient has subsequently been examined on an average of every three months to August, 1942, at which time the vaginal mucosa was smooth and the rectum was healed with slight constriction of the lumen of the rectum.

DR. HERBERT E. SCHMITZ, CHICAGO, ILL.—This condition is not as rare as we are led to believe by the author's statements. If routine cystoscopic and proctoscopic examinations were done at one-, two-, or three-year intervals many cases of telangiectasia of the bladder and rectal mucosa would be found. Oftentimes symptoms due to these changes are not called to the attention of the physician.

The use of interstitial irradiation will increase ulceration of both the bladder and the rectum. Great care must be taken in packing these areas away from the source of irradiation, and we must remember when using multiple sources of radia-

was made in August, 1936. Treatment by radium and roentgen rays was instituted. In June, 1937, she complained of diarrhea, rectal pain, passage of eight to ten stools a day, and occasionally bloody mucous discharge. The diarrhea changed to a fairly regular bowel habit but the bloody mucous discharge continued.

Proctoscopic examination in June, 1938, disclosed factitial proctitis with an area of ulceration measuring 1 by 2 cm. on the anterior rectal wall at a distance of 8 cm. from the dentate margin. This patient was examined with the proctoscope four times thereafter, the last time in May of 1941, when slight contraction of the lumen of the rectum was noted. The ulcer had healed. The rectal wall was the site of telangiectasis that produced slight bleeding when traumatized. The patient was essentially free of rectal symptoms.

Treatment

Except in those few cases in which ulceration is sufficient to lead to formation of fistula, or in the occasional case wherein actual involvement of the rectovaginal septum by the malignant process is responsible for breakdown of the tissues, healing will take place, providing the patient survives the malignancy for a sufficient time. Healing is accompanied by scarring, occasionally some reduction in the size of the lumen of the rectum and by telangiectasis which usually produces bleeding from the rectum. In cases in which strictures develop obstruction will not occur unless extension of the malignancy has been the cause of this stricture. Strictures resulting from proctitis do not offer a therapeutic problem very frequently.

Usually colostomy has not been considered part of the treatment of factitial lesions of the rectum. Those patients whom we have observed, on whom this operation has been performed, have obtained little relief from the pain, tenesmus and bloody mucous discharge.

Usually the patients can be taught proper care of the rectum. It should be explained to them that time is one of the most necessary factors to be considered and that treatment usually is prolonged. The patient should take a warm, cleansing enema after each defecation in order to keep the rectum as free from fecal matter as possible. She is then instructed to inject 2 fluidounces (60 c.c.) of warm hamamelis water (witch hazel), to be retained until the next movement of the bowel. Often the injection of 2 fluidounces of warm olive or mineral oil before retiring is of benefit. A bland diet, re-enforced with some substitutes to furnish bulk, such as are now available, allows a soft stool free from irritating particles. Caustic medicaments should not be applied.

The physician who must treat inoperable carcinoma of the female genital tract is confronted with a serious problem. His aim is to cure the malignancy or, if this is impossible, to obtain as much palliation as possible. In order to accomplish these effects he must irradiate the tumor intensively and yet afford the maximal protection to the neighboring

The patient to whom Dr. Coventry referred is one of the more fortunate individuals who have had colostomy performed. In those patients that we have seen in whom this operation has been performed, by no means all of them obtained the relief that had been anticipated.

Patients who have factitial changes in the rectum are frequently told that they have cancer in the rectum. In the group that we report this was true in only one instance, that of a case who had had a primary carcinoma of the vagina.

We were moved to write this paper to emphasize the fact that factitial changes are very common and must be accepted as one of the risks of adequate treatment of carcinoma of the uterine cervix.

tion that the beams may cross giving us a much higher dose of irradiation in the bladder or rectum than we are attaining in the lesion itself.

DR. WILLIAM A. COVENTRY, DULUTH, MINN.—I would like to report a case with this condition in which the patient had been maltreated before she came into my hands. She came from a small town in Wisconsin and had been treated by a country practitioner. She had been given, according to her story, 6,000 mg. hours of radium in the uterus and 1,200 mg. hours in the cervix some three months previously. When I first saw her she had an ulcer adjacent to the cervix and was almost a confirmed addict to morphia because of the severe pain. I attempted to treat her locally for three or four weeks, but the morphia habit and pain were getting worse and I then did a colostomy in order to put the rectum at rest. The pain disappeared in a week after I had diverted the fecal contents through the colostomy. She at that time developed a rectovaginal fistula at the site of the ulcer. In about three months the ulcer and rectovaginal fistula healed spontaneously and six months afterward I closed the colostomy. The patient has been observed for the last four years, and there is no sign of a return of the trouble. She gave up the morphia and gained in weight.

DR. FREDERICK S. WETHERELL, SYRACUSE, N. Y.—With the formation of many tumor clinics we are going to have more and more difficulties of the kind to which Dr. Randall has called attention. Radium in the minds of many men is merely a substance within a capsule which may be put into the cervical and uterine canal and left there for a certain number of hours to work a miracle. Sight is lost of the fact that it is distance, not filtration, which limits the action of the gamma ray, which explains the need for thick packs to displace rectum and bladder.

We as a Society should make a continued effort to limit the use of radium to men who are trained and who understand the physics of radium. A minor point in technique to many is the need of adaptation of the clinical picture to the method of dosage. Bowing of the Mayo Clinic, whose technique I have followed for twenty-two years, has had few cases of proctitis, due to the fact that he leans very much to the fractional method rather than the massive dose which was so prevalent twenty-two years ago. The only case of severe proctitis which I have seen was one which was treated entirely by x-ray, with a million volt machine. It was an advanced case and had been treated from the clinical experimental angle, quite properly.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—Usually the best treatment of a severe irradiation burn is to cut out the burned area and implant a graft or flap of normal tissue. As such burns are precancerous lesions it would seem unwise to permit a patient to continue indefinitely with a severe irradiation proctitis. In a woman of 26 seen last year, a colostomy had finally been done to relieve the obstruction and local distress following intense irradiation for carcinoma of the uterus. The patient also did not wish to marry with a permanent colostomy, so we took out the remainder of the rectum, liberated the colostomized segment of the sigmoid and pulled it through the anus and closed the abdominal wound. This was a decided improvement. The possibility of a secondary cancer in the rectum, we believe, has been eliminated, the new anal opening is functioning and a very fair degree of control has developed, so that the patient need not wear a pad while the stools are formed. I would advise an operation of this type for another similar affliction.

DR. RANDALL (closing).—I believe that a majority of patients who have received treatment with radium and roentgen rays for carcinoma of the uterine cervix have factitial changes in the rectum. The group reported by us had sufficient symptoms to justify investigation by means of proctoscopic examination.

gen, diethylstilbestrol,* were employed. Estradiol was administered intramuscularly, and estriol glucuronide and diethylstilbestrol were given orally. Their administration was of cyclic order, i.e., from the fifth to the fourteenth day of the cycles of 5 patients, and from the fifth to the twenty-fourth days of the cycles of 11 patients. Daily dosages varied: those of estradiol benzoate from 0.33 to 0.67 mg.; those of estradiol dipropionate 2.5 mg. every other day; those of estriol glucuronide from 1,800 to 4,800 oral units; and those of diethylstilbestrol from 1 to 3 mg.

Six patients received treatment during 1 cycle; 6 patients during 2 consecutive cycles; and 4 patients received treatment during 3, 4, 5, and 8 consecutive cycles, respectively.

Endometrial biopsies were done prior to, during, and after therapy. These biopsies were secured uniformly within the first twenty-four hours after the onsets of bleeding. Classification of endometrial responses was done by one of us (E. C. H.).

Data upon the lengths of the cycles and the durations and amounts of bleeding before, during, and following therapy were analyzed.

All patients had complete medical, gynecologic, and endocrine surveys, including determinations of the basal metabolic rate and roentgenograms of the sella turcica.

Data

The immediate effects of therapy were studied in 39 cycles. Following the cessation of treatment; clinical data upon 24 additional cycles were evaluated.

1. *Dosage Schedules.*—The therapeutic schedules employed and the related endometrial responses are detailed in Table I.

TABLE I. THERAPEUTIC SCHEDULES AND RELATED ENDOMETRIAL RESPONSES

	PATIENTS	CYCLES	ENDOMETRIAL FINDINGS	
			ESTROGENIC	PROGESTATIONAL
Estradiol benzoate:				
0.33 mg. 5th to 14th days inclusive	4	8	5	0
0.67 mg. 5th to 14th days inclusive	2	2	1	0
Summary:		10	6	0
Estradiol dipropionate:				
2.5 mg. every other day				
5th to 29th days inclusive	1	1	1	0
Estriol glucuronide:				
1,800 o.u. 5th to 24th days inclusive	1	1	1	0
2,400 o.u. 5th to 24th days inclusive	2	3	3	0
4,600 o.u. 5th to 24th days inclusive	1	1	0	1
4,800 o.u. 5th to 24th days inclusive	2	2	2	0
Summary:		7	6	1
Diethylstilbestrol:				
1 mg. 5th to 14th days inclusive	4	5	3	0
1 mg. 5th to 24th days inclusive	2	2	0	1
2 mg. 5th to 24th days inclusive	8	11	4	2
3 mg. 5th to 24th days inclusive	2	3	2	0
Summary:		21	9	3
Total: 39 cycles of therapy; 26 endometrial studies, 22 estrogenic and 4 progestational.				

*Diethylstilbestrol (estrobene) supplied by Ayerst, McKenna and Harrison, Montreal, Canada.

EFFECTS OF ESTROGENIC THERAPY UPON OVARIAN FUNCTION*

II. When Employed During Anovulatory Cycles

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THE ability of adequate estrogenic therapy to transform normal progestational cycles of women to estrogenic (and presumably anovulatory) ones has been verified in the preceding communication.¹ It would appear most unlikely that therapy of this kind and order is capable of restoring normal progestational cycles in women with ovarian failure of anovulatory type.

An investigation, however, of the end results of estrogenic therapy in association with anovulatory failure seemed advisable for several reasons: (1) to confirm or to deny the dictum that, regardless of our ability to substitute for the endocrine deficiency of ovaries with intrinsic ovarian principles no salvage of physiologic functions, i.e., return of the fertile state, results; and (2) to confirm or to deny the theory that the salvage of ovarian function which has been described as following cyclic estrogen-progesterone therapy in a large group of women with prolonged or excessive estrogenic bleeding results solely from the estrogenic fraction of the therapeutic schedule. The commercial availability of a cheap, potent, and orally active nonhormonal estrogen (diethylstilbestrol) requires a clear definition of the role of estrogens in the treatment of ovarian failure.

Methods

Sixteen patients whose ages ranged from 15 to 35 years (average age 21.6 years) were selected for this investigation. These patients had presumed anovulatory ovarian failure predicated upon the occurrence of episodes of estrogenic bleeding. The bleeding cycles were commonly irregular and often of prolonged duration. Each patient selected had received from one to three endometrial biopsies prior to initiation of therapy.

Two hormonal estrogens, estriol glucuronide† and estradiol in the form of its benzoate‡ and dipropionate,§ and an nonhormonal estro-

*Part I of this article was included in the February issue.

†Estriol glucuronide (emmenin) supplied by Ayerst, McKenna and Harrison, Montreal, Canada.

‡Estradiol benzoate (progynon-B) supplied by Schering Corporation, Bloomfield, N. J.

§Estradiol dipropionate (di-o-oeylin) supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Few endometrial studies were made following cessation of therapy due to the fact that the majority of the patients were transferred to other therapeutic regimen. Three follow-up endometrial samples, however, were taken on two patients; all were estrogenic.

3. *Effects Upon the Lengths of the Cycles.*—The characteristic effect was a reduction in the cycle lengths to within normal limits: the average lengths of cycles prior to treatment were 49.2 days and during therapy 28.7 days. This effect was apparent in the first treatment cycles which averaged 33.1 days in length. In 2 instances, however, estradiol therapy was followed by absence of expected episodes of bleeding with sequential doubling in the lengths of the cycles. Both of these exceptions occurred during first treatment cycles and are included in the above average of 33.1 days.

Following the cessation of treatment, data on 6 patients indicated a regression from the established normal cycle lengths, the average becoming 48.5 days.

4. *Effects Upon the Duration and Amount of Uterine Bleeding.*—The average duration of bleeding decreased from 18.4 days prior to treatment to 6.2 days during therapy. This alteration was immediately apparent in the first episodes of bleeding which occurred during therapy.

Episodes of bleeding following cessation of therapy averaged 7.2 days. During the cycles studied after therapy only 1 patient had a recurrence of prolonged bleeding. This occurred at the termination of the second cycle which followed the cessation of therapy. This patient had received only 1 cycle of diethylstilbestrol therapy, 2 mg. daily, from the fifth to the twenty-fourth days, inclusive.

Prior to therapy an average of 46 well saturated sanitary pads were used per episode of bleeding, during therapy 13, and following cessation of treatment, 15 per episode of bleeding. The reduction in the total number of pads used by these patients during treatment paralleled the decrease in the duration of bleeding.

5. *Effects Upon Withdrawal Time.*—An episode of bleeding was defined to be due to estrogen withdrawal if it occurred within a few days after cessation of therapy and considerably in advance of the expected date of bleeding. In 6 treatment cycles of 4 patients the withdrawal time averaged 4.5 days, the range being from two to eight days. Three of these patients had received estradiol benzoate during the first half of the cycle while the fourth patient had received diethylstilbestrol during the same interval.

Discussion

There is little evidence from the data presented that the use of moderately small doses of hormonal or nonhormonal estrogens exerts stimulative or restorative effects upon the disturbed ovario-endometrial status of anovulatory ovarian failure. Of 26 endometrial responses studied during therapy 22, or 84.6 per cent, were estrogenic.

The 4 progestational responses encountered in the instances of 2 patients warrant discussion. The therapeutic schedules of these 2 patients have two things in common: (1) They were of greatest length (5 and 8 consecutive cycles); and (2) they comprised 3 consecu-

2. *Effects Upon the Endometrium.*—Endometrial studies were made during 26 of the 39 cycles of treatment of 12 patients. These findings are detailed in Table II. Twenty-two (84.6 per cent) of the 26 endometrial responses remained estrogenic. The 4 progestational endometriums encountered were in the cases of 2 patients, 3 in one instance and 1 in the other. One of these patients had progestational responses during the sixth, seventh, and eighth cycles of therapy (Fig. 1). All of her previously studied endometriums had been estrogenic. She had received previously estriol glucuronide, but at the time of her positive responses she was receiving diethylstilbestrol. The other patient had a progestational response after the fourth consecutive cycle of therapy with estriol glucuronide. Her 3 preceding cycles had been characterized by estrogenic endometriums.

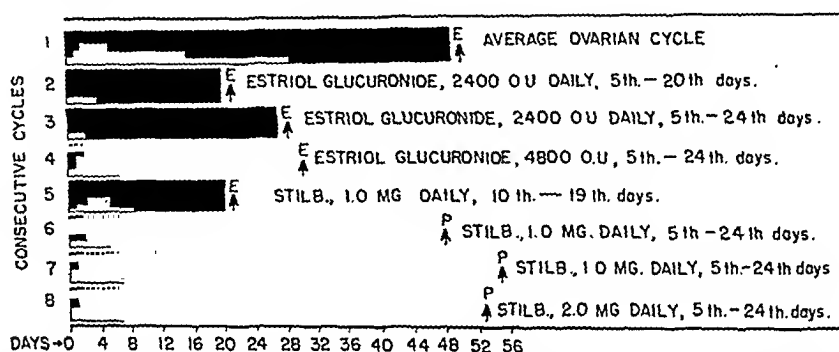


Fig. 1.—Effects of therapy with estriol glucuronide and diethylstilbestrol in 7 consecutive bleeding cycles of Patient 15. Episodes of bleeding are represented for each cycle at the left of the graph. Stilb., signifies diethylstilbestrol.

TABLE II. ENDOMETRIAL RESPONSES DURING AND AFTER THERAPY*

CASE	SERIES OF THERAPY	CONSECUTIVE CYCLES STUDIED							
		1	2	3	4	5	6	7	8
1	1	edb-O	edb-E	edb-O	ORx-E	ORx-O			
2	1	edb-E	ORx-O	ORx-O					
3	1	edb-E	edb-E	ORx-O	ORx-O	ORx-O	ORx-O	ORx-O	ORx-O
4	1	edb-E	edb-E	ORx-O					
5	1	stb-E	stb-O						
6	1	stb-O							
7	1	stb-O	stb-E	stb-O	stb-E+				
8	1	stb-O	ORx-O	ORx-O					
9	1	stb-O							
10	1	stb-E	stb-E+						
11	1	stb-E	stb-E						
12	1	stb-E							
13	1	edb-O	stb-O						
14	1	edd-E	ORx-E	ORx-O	ORx-O	ORx-O	ORx-E-		
	2	stb-O							
15	1	edb-O	es-E	es-E	es-E	stb-E	stb-P-	stb-P-	stb-P
16	1	es-E	es-E	es-E	es-P	stb-O			

*Therapy

edd, Estradiol dipropionate
 edb, Estradiol benzoate
 es, Estriol glucuronide
 stb, Diethylstilbestrol
 ORx, No therapy, but data on cycle and bleeding obtained

Classification of Endometrial Responses

E-, Minimal estrogenic response
 E, Moderate estrogenic response
 E+, Marked or hyperestrogenic response
 P-, Minimal (immature) regular progestation
 P, Normal progestation
 O, No biopsy

2. Therapy of this kind and order regulates the cyclicity and duration of flowing probably by direct alterations in the functional capacities of the endometrial vessels.

3. The regulatory action of cyclic estrogen-progesterone therapy is due primarily to effects of the estrogen fraction.

4. The salvage of physiologic function which occurs in many patients with estrogenic flowing following therapy with the cyclic estrogen-progesterone schedule is dependent upon the progesterone fraction.

5. The one-two administration of and the synergism between estrogens and progesterone are important facets of the combined therapy.

6. Salvage, when it occurs, probably is due to the ability of this complementary therapy to prevent progress of ovarian failure and to favor spontaneous recovery of normal function.

Part of the expenses of these studies was defrayed by grants to one of us (E. C. H.) from the Research Council of Duke University, from Ayerst, McKenna and Harrison, Ltd., Montreal, Canada, and from Schering Corporation, Bloomfield, N. J.

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THE MANAGEMENT OF OVARIAN TUMORS IN ELDERLY WOMEN*

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SURGERY in elderly women, especially in the seventh, eighth, and ninth decades of life, is attended with considerable risk. Many such patients present themselves at a hospital or a clinic with ovarian tumors, but because of their age or poor physical condition, they are denied the benefits of surgery. Although most gynecologists agree that the only chance these patients have to be cured is by operation, frequently they feel that the additional life expectancy does not warrant the procedure. Our experience at Kings County Hospital has been at variance with this. We present, therefore, a brief summary of our results in the management of ovarian tumors in women past the menopause.

From Jan. 1, 1935, through July 1, 1942, a period of seven and one-half years, 13,010 patients were admitted to the gynecologic service of the Long Island College Division of the Kings County Hospital. Of this number, 344, or 2.6 per cent, had ovarian tumors. Pathologic study revealed practically all varieties (Table I), and 262, or 76.2 per cent, were benign, while 82, or 23.8 per cent, were malignant. Eighty-

*Read at a meeting of the Brooklyn Gynecological Society, Nov. 6, 1942.

tive cycles of estriol glucuronide therapy. The progestational response of one patient followed the third cycle of estriol glucuronide therapy but did not recur in the succeeding cycle of diethylstilbestrol therapy. The 3 progestational responses of the other patient occurred during the second, third, and fourth consecutive cycles of diethylstilbestrol therapy, which were sequential to the treatment with estriol glucuronide. These progestational responses may be regarded as being the results of intercurrent recovery of ovarian function or one may relate their incidence to a specific virtue of prolonged therapy with estriol glucuronide. Therapeutic schedules of this kind and order warrant further study.

The estrogenic therapy was observed to regulate quite uniformly the cyclicity and duration of flowing. The majority of the patients studied had lengthened cycles (average 49.2 days) and prolonged flowing (average duration 18.4 days) prior to institution of therapy. During therapy the cycle lengths were reduced to an average of 28.7 days and the durations of bleeding episodes to an average of 6.2 days.

From these studies, it seems reasonable to relate chiefly the regulatory effects of cyclic estrogen-progesterone therapy in prolonged or excessive estrogenic bleeding to specific effects of the estrogen fractions on the endometrial vascular system. The ultimate salvage, i.e., return of progestational cycles, which has been related to this cyclic combined therapy seems dependent upon the one-two sequential use of and the synergism existing between estrogen and progesterone. It is doubtful that any direct stimulative effects upon ovarian function result but rather it is likely that intercurrent recovery is facilitated and progression of ovarian failure prevented by the regulatory actions of this therapy on the functional capacities of the endometrial vascular tree and the pituitary.

Summary and Conclusions

Moderately small doses of hormonal estrogens (estrone, estradiol benzoate and dipropionate, and estriol glucuronide) and of a nonhormonal estrogen (diethylstilbestrol) were administered cyclically to 16 women who were experiencing anovulatory ovarian failure predicated upon the occurrence of prolonged and excessive estrogenic bleeding. Twenty-two of the 26 (84.6 per cent) endometrial biopsies studied during therapy continued to be of estrogenic nature. The 4 progestational responses, which were encountered in 2 patients, were related to prolonged therapy with estriol glucuronide and were judged to be evidence of intercurrent recoveries of function. Satisfactory regulation of the cyclicity and duration of flowing was credited to the cyclic estrogenic therapy.

The following conclusions are judged warranted:

1. The cyclic administration of moderate doses of hormonal and nonhormonal estrogens resulted in no direct stimulative effects upon ovaries in anovulatory failure.

selected is the simplest and most rapid which will eliminate the pathology. To avoid the ill effects of general anesthesia, local anesthesia is used exclusively.

Procedure

All patients are premedicated with twilight sleep (morphine sulfate and scopolamine hydrobromide), the dose being determined for each individual according to age, general body configuration, and physical condition. The average dose required was a total of one-third grain of morphine sulfate and one one-hundredth grain of scopolamine hydrobromide given in divided doses. In only a few instances was it necessary to resort to supplemental inhalation anesthesia. Local anesthesia demands extreme gentleness and care in the handling of tissues, and this, we believe, is ideal for such patients. If the patient's condition is satisfactory at the close of the operation, closure of the abdominal wall is performed in layers using interrupted, nonabsorbable, fine sutures (silk or cotton). This method of closure requires minimal handling of tissues and results in little or no local tissue reaction. However, if the patient's condition is poor, the abdominal wall is closed with heavy through-and-through, nonabsorbable sutures that are carried through all the layers from peritoneum to skin, inclusive. Postoperatively, the prevention and early treatment of distention lessens cardiac embarrassment and discomfort. Prostigmine is used routinely for this purpose. Fluids and food by mouth are started within a few hours after the patient's return to bed. Only in rare instances have we had to use cardiac stimulants other than digitalis. The patient is encouraged to move her legs and is not permitted to remain in one position for more than an hour. All efforts are made to get her out of bed as soon as possible. This has been facilitated by the careful closure of the abdominal wall with nonabsorbable sutures, supplemented by a good abdominal binder.

To illustrate these principles, we have chosen the following typical case:

Case Report

Mrs. J. A., a 65-year-old, white housewife, was admitted to the gynecologic service of the Long Island College Division of the Kings County Hospital on April 25, 1938, complaining of progressive abdominal enlargement and left lower quadrant pain, accompanied by marked urinary frequency. These symptoms had been present for two months. Her menopause occurred fifteen years before, and since then she has had no bleeding or vaginal discharge. The significant findings on physical examination were an elevated blood pressure (160/85), a moderately enlarged heart with a systolic murmur at the apex, and a large, cystic, indefinite mass which arose from the pelvis and filled the lower half of the abdomen. After preliminary study and bed rest for ten days, during which time she was digitalized, laparotomy under twilight sleep and local anesthesia was performed. A 20 cm. multilocular, pseudomucinous ovarian cyst was removed and the abdomen was closed in layers with fine black silk. The total operating time was fifty minutes. Her postoperative course was uneventful. The highest temperature was 100.6° F. on the second postoperative day. She was allowed out of bed on the fifth day and discharged as cured on May 21, 1938, sixteen days after the operation.

eight, or more than one-fourth of the patients, were fifty years of age or older, while 10 were more than sixty-five years (Table II). In the postmenopausal group, 27, or 30.7 per cent, of the tumors were benign while 51, or 69.3 per cent, were malignant.

TABLE I. CLASSIFICATION OF OVARIAN TUMORS

TYPE OF TUMOR	TOTAL	POSTMENOPAUSAL	
		NUMBER	INCIDENCE (%)
<i>Benign:</i>			
Simple serous cystadenomas	196	24	12.3
Papillary serous cystadenomas	5	2	40.0
Pseudomucinous cystadenomas	21	5	23.8
Dermoid cysts	32	2	6.3
Fibromas	4	1	25.0
Granulosa cell tumors	2	2	100.0
Thecomas	1	1	100.0
Brenner cell tumors	1	0	0.0
Total	262	27	30.7
<i>Malignant:</i>			
Adenocarcinomas	78	47	60.3
Krukenberg tumors	4	4	100.0
Total	82	51	62.2
Grand Total	344	88	25.6

TABLE II. AGE INCIDENCE

	51-60		61-70		71-82	
	BENIGN	MALIGNANT	BENIGN	MALIGNANT	BENIGN	MALIGNANT
Number	16	36	5	19	6	6
Incidence	18.2	39.8	5.7	21.6	6.8	6.8

From this it is apparent that more than one-fourth of the women admitted to our institution with ovarian tumors after the menopause could be cured by surgery, provided the procedure was carried out with a minimum of shock and trauma, either from the operative procedure itself or from anesthesia. It is true that in this age group, patients are frequently more prone to have chronic cardiovascular, pulmonary, or renal diseases, but these complications have not been sufficient to contraindicate an attempt at surgical removal of the ovarian mass.

In the management of such patients, three cardinal principles must be adhered to: (1) careful, preoperative preparation; (2) rapid operation with minimum trauma; (3) early return to activity.

To evaluate the surgical risk, close cooperation with the department of medicine is maintained. Routine preoperative chest plates, electrocardiograms and detailed renal function studies are essential. A preliminary period of bed rest is often necessary; in several of our cases, a period of two months was employed. Where necessary, transfusions, and fluids should be liberally given. Digitalis is administered for signs of decompensation or myocardial damage. Careful watch of the blood count, sedimentation time, and the temperature determine the optimum time for surgery, and, when this time arrives, the operative procedure

PATHOLOGY OF POSTMENOPAUSAL BLEEDING*

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THIS report is based on the pathologic findings in women 50 years or older, or past the menopause, who presented themselves at the Kings County Hospital, Long Island College of Medicine Division, for vaginal bleeding, spotting, or staining. It includes all specimens in the above category, received in our laboratory from December, 1939, to December, 1941. The total number of specimens reported is 114, selected from over 2,000 gynecologic specimens received during this period. Clinical consideration, other than brief mention, is beyond the scope of this paper.

The minimum age limit of 50 is selected to avoid bleeding due to fibroids, and to study the pathology of the endometrium in this age group. Only a short discussion will be devoted to the malignancies encountered in this survey; the remainder of the report will be concentrated on benign causes for postmenopausal vaginal bleeding, or bleeding in women past 50.

There were 42 cases of malignancy representing 36.8 per cent of the total; 23 were carcinoma of the cervix (20.2 per cent) and 19 were carcinoma of the corpus (16.7 per cent). In two patients, vaginal bleeding was associated with ovarian tumors; one, in a patient aged 61 years, was a thecoma, and the other, in a patient aged 53, was a papillary adenocarcinoma. In addition, 6 cases were associated with extra uterine pathology; 3 metastatic malignancies from unknown origins, one neurogenic sarcoma, one carcinoma of the vulva, and one mixed mesodermal tumor of the uterus. The total incidence of malignant lesions equals 43.1 per cent (corrected for one benign ovarian tumor).

In the remaining 65 cases (56.9 per cent excluding the thecoma), vaginal bleeding was either associated with benign lesions of the endometrium or cervix, or no demonstrable cause was evident.

There were 6 cases of endocervicitis; one associated with endometrial hyperplasia, and the etiology for the bleeding was ascribed to the hyperplasia. There were 5 cases of benign cervical polyps, and 4 of endometritis.

In 10 instances, insufficient material was obtained for diagnosis; nevertheless, these women had vaginal bleeding. In one, the diagnosis was found to be an adenoma malignum after the uterus was obtained.

Atrophic endometrium was diagnosed twice. One was associated with a large endometrial polyp presenting hyperplastic changes, and this readily accounted for the bleeding; this patient was 50 years old. The

*Read at a meeting of The Brooklyn Gynecological Society, November 6, 1942.

Results

The results of this routine have been most gratifying to us. There were no mortalities among the 25 women operated upon where benign neoplasms were found. Two patients died before operation, one from bronchopneumonia and the other from cardiac failure. Many of these women have been followed for five or more years and at present are well and asymptomatic. As is to be expected, the mortality was considerably higher in the group of 51 malignancies. However, the immediate post-operative failures were comparatively few. Only three patients failed to survive the immediate postoperative period. One patient died from renal insufficiency, the second from bronchopneumonia on the eighth postoperative day, and the third from cardiac failure. More than half of the patients followed (57.6 per cent) died within five years. Nevertheless, considering the fact that most of these women were originally sent to the Kings County Hospital for terminal care, since operation was deemed impossible or foolhardy, even this low salvage rate is worth while.

Consequently, before condemning an elderly woman with an ovarian tumor to a short life of chronic invalidism, it behooves the physician to remember that in our experience, one-fourth of the patients had benign lesions, although the preoperative diagnosis was usually ovarian malignancy. With proper caution, such women were returned to a normal, active, self-sustaining life to which at least five years have been added. To refuse the benefits of surgery to an elderly woman purely on the basis of her age or moderately poor physical condition, in our opinion, is not justified.

Summary

1. A brief summary of 344 cases of ovarian tumor is presented.
2. Attention is called to the fact that in 88 neoplasms found in women of fifty or more years of age, 30.7 per cent were benign, and with proper precautions, they were successfully removed.
3. The routine for the care of this group is outlined.

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In 1941, Novak and Richardson, Jr.,³ reported 137 cases of postmenopausal endometriums; 62 were diagnosed as atrophic, 14 moderately proliferative, 28 actively hyperplastic, and 33 were of the retrogressive hyperplastic type ("Swiss-cheese" pattern with a low atrophic epithelium and a fibrous stroma).

Geist and Matus,⁴ in 1933, in a series of 182 cases of postmenopausal bleeding found that 42 per cent were benign. Ovarian neoplasms were found in 10; 29 were due to polyps; 10 associated with hyperplasia; 11 were inflammatory (endometritis or endocervicitis); 15 had fibroids; 3 had adenomyosis, and 13 were negative.

Our findings are not consistent with those cited above nor with other reports in the literature. The percentage incidence of malignancy and the number of specimens diagnosed as atrophic endometriums in our series is appreciably less.

TABLE II. SUMMARY

	NUMBER OF CASES REPORTED	MALIGNANT LESIONS (PER CENT)	BENIGN LESIONS (PER CENT)
Kanter and Klawans ⁵	98	68.4	31.6
Brown ⁶		66.8	33.2
Schulzer ⁷		68.0	32.0
Geist and Matus ⁴	182	57.5	42.5
Norris ⁸		53.3	46.7
Taylor and Millen ²	406	63.3	36.7
Te Linde ⁹		53.3	46.7
Geiger ¹⁰	395	81.3	18.7
Schwartz (1942)	114	43.1	56.9
Average		61.6	38.4

Discussion

Bleeding from an endometrium that is neither being sensitized, nor undergoing cyclic changes because of cessation of ovarian function, is an interesting phenomenon and at present has not been satisfactorily explained. It is true that many are associated with malignant growths, and in a relatively large group the underlying factor may be an inflammatory process or a benign neoplastic growth, or as has been shown above, no lesion whatever can be demonstrated.

The exact cause for the activity of the endometrium in elderly women is not understood, since the source of postmenopausal estrogen is not precisely known. Regressive changes and diminished function in the ovary occur before the menopause becomes evident. Scars and furrows on the ovary increase in number as follicles rupture and are transformed to corpora lutea and corpora albicantia. The number of mature follicles decreases and the atretic follicles regress and occasionally leave small scars.

Blood and urine assays of ovarian hormones during the climacteric have been reported, but no complete study of secretion and excretion of these hormones during this entire period has been carried out. It is generally accepted that secretion of estrogens diminishes up to the menopause, and thereafter continues at a much reduced level.

other was in a 60-year-old woman who had an endocervicitis which probably caused the anomalous bleeding.

In 21, the findings were those of a cyclic mucosa: 15 were in the proliferative and 6 were in the secretory phase. Of these, 7 were associated with endometrial polyps, 5 with fibroids, and 2 with malignancies of the cervix. The ages of these patients varied between 45 and 60 with an average of 51. They were five months to five years past the menopause. Endometrial polyps alone were found in 8 cases; in 5, concomitant hyperplasia of the endometrium was found with the polyps.

A striking finding in this series was 8 cases of endometrial hyperplasia representing 7.0 per cent of the total. The ages of the patients varied between 47 and 81 with a mean of 55 years, and the patients were 15 months to 30 years postmenopause. The bleeding was usually more constant and more profuse, and varied over a period of time. The cause for hyperplasia in elderly women is speculative, as is the reason for cure of their vaginal bleeding by curettage.

TABLE I. MALIGNANT LESIONS

	NUMBER OF CASES	INCIDENCE (PER CENT)
Carcinoma of cervix	23	20.2
Carcinoma of corpus	19	16.7
Metastatic malignancy of uterus	3	2.6
Mixed mesodermal tumor of uterus	1	0.9
Malignancy of ovary	1	0.9
Carcinoma of vulva	1	0.9
Neurogenic sarcoma	1	0.9
Total	49	43.1

TABLE II. BENIGN LESIONS

	NUMBER OF CASES	INCIDENCE (PER CENT)
Cyclic mucosa, -	21	18.4
proliferative, ..	15	13.2
secretory	6	5.2
Undetermined	10	8.8
Endometrial hyperplasia	8	7.0
Endometrial polyps	8	7.0
Endocervicitis	6	5.2
Cervical polyps	5	4.3
Endometritis	4	3.5
Atrophic mucosa	2	1.8
Benign ovarian tumor (thecoma)	1	0.9
Total	65	56.9

Breipohl,¹ in 1935, reported a study of 130 postmenopausal endometriums. A large number showed changes of the atrophic type; adenocarcinoma was seen in 22; 31 were proliferative, of which 15 were hyperplastic (including 2 granulosa cell carcinomas), and 3 secretory.

Taylor and Millen,² in 1938, found 63 per cent of postmenopausal bleeding associated with some form of carcinoma. Included in their series of benign lesions of the endometrium were 74 cases diagnosed as atrophic mucosa, and 11 as hyperplasia (4 of these were associated with granulosa cell tumors).

RÉSUMÉ OF CARDIAC DISEASE IN PREGNANCY FOR A FIVE-YEAR PERIOD*

With Report of a Case of Coarctation of the Aorta

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IN REVIEWING the chronic cardiac patients among the pregnant women cared for on our service at this hospital during the past five years, we find from Table I that they numbered 102 out of a total of 5,664 deliveries, or 0.18 per cent.

TABLE I

	CARDIAC CASES	WARD	PRIVATE	SECTIONS	INTER- RUPTED	DEATHS
1937	23	17	6	1	0	1
1938	30	22	8	3	1	0
1939	21	13	8	0	1	0
1940	12	9	3	3	0	0
1941	16	11	5	0	3	0
Total	102	72	30	7	5	1

Ninety-six of the 102 were delivered from below, usually by low forceps to shorten the second stage in both multiparas and primiparas alike. Seven were delivered by cesarean section. Of the seven cesarean sections, one was private and six were service patients. Four were primiparas and three multiparas. Two were repeat sections. Indications were active chorea and rheumatic heart disease, previous decompensation, coarctation of the aorta, marked cardiac enlargement with double lesion and probability of very long labor in a primipara with double lesion. There were three therapeutic interruptions in the first trimester, two by abdominal hysterotomy with sterilization, and one from below. There was one death. This followed cesarean section under local, supplemented by cyclopropane anesthesia and was due to pneumonia. There have been two general trends evident in our handling of these cardiac patients. One, the tendency to deliver more and more cardiac patients from below rather than by section. Two, the tendency to substitute cyclopropane anesthesia for the time-honored open drop ether in cases delivered from below, and local in sections.

The most unusual of these cases was one of coarctation of the aorta, and as only 29 cases of this complication in pregnancy had been reported in the literature up to 1940, it was thought that a report of our case might be of interest.

*Read at a meeting of the Brooklyn Gynecological Society, October 6, 1942.

The ovary is not capable of spontaneous reactivation after the menopause, and, therefore, some other mechanism or source must be found for the estrogens. Of all the possibilities, two seem most likely. The estrogenic sex sterols are chemical metabolites of certain body sterols with cholesterol as the mother substance of the estrogens. Or an extraovarian endocrine gland, most likely the follicle-ripening gonadotropic hormone of the anterior pituitary may be the source. In favor of the latter is the presence of the estrin factor in the urine of castrated women, but this evidence is only presumptive and has a wide individual variation.

Conclusion

The varied histology of the endometrium after the menopause reflects the variation in the terminal functional activity of the ovary. If menstruation and ovulation end together and abruptly, the endometrium will be of the atrophic type. If the terminal cycles are anovulatory, the hyperplastic pattern may exist even in the absence of postmenopausal bleeding. After estrogenic production ceases, the pre-existing hyperplasia may show marked regressive changes in the epithelium and stroma.

Summary

1. The pathology of 114 specimens from women past the menopause or over 50 years of age who had anomalous bleeding is reviewed.
2. The percentage of benign lesions of the endometrium or cervix is 56.9, and the percentage of malignancy is 43.1.
3. Endometrial hyperplasia represented 7.0 per cent of the total.
4. The cause for postmenopausal bleeding cannot always be determined.
5. The histology of the postmenopausal endometrium depends on the terminal functional activity of the ovary.

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Blood studies were recorded as follows: Hemoglobin, 70 per cent; red blood cells, 3,500,000; white blood cells, 5,000 with 82 per cent polymorphonuclears and 18 per cent lymphocytes; Blood urea 14.2 mg. per 100 c.c., creatinin 0.59 mg. and sugar 75 mg. The sedimentation rate was 36 mm. in $\frac{1}{2}$ hr. and 73 mm. in 1 hr. The circulation time with patient in the recumbent position and using 5 c.c. of decholin injected into the right antieubital vein was 12 sec. (normal 14 to 16 sec.). The same amount in the ankle vein was 32 seconds.

Except for slight stiffness and narrowing of the veins, the eye grounds were negative.

Six days after admission, a low flap cesarean section and Pomeroy sterilization were performed. A living male infant weighing 7 pounds and 8 ounces was delivered. Pitocin was used as an oxytocic. Pre-operative medication consisted of 3 grains of seconal and $\frac{1}{150}$ grain of atropine. Local infiltration and block anesthesia using $\frac{1}{2}$ per cent novocain without adrenalin were used and supplemented by intravenous sodium pentothal. The blood pressure, which at the beginning of the operation was 210/100, dropped to 138/62 after the first few minutes, but soon rose to 180/110, at about which level it remained throughout the operation.

Before closing the peritoneum, the operator palpated the abdominal aorta and reported that it measured approximately 1 cm. in diameter throughout its entire length.

The postoperative course was uneventful except for a slight fever beginning on the eighth day and subsiding on the thirteenth, and was accompanied by foul lochia. She was allowed out of bed on the seventeenth postoperative day and home on the twentieth.

Summary

This condition is found two to three times more frequently in females than in males. It is usually a congenital anomaly, though the adult type has been reported as a result of *Streptococcus viridans* infection. The lesion itself is a narrowing or constriction of the aorta in the region of the insertion of the ductus arteriosus or its vestige. In 25 per cent of these cases, the aortic valve is bicuspid. This gives rise to a narrowing of the lumen and thinning of the walls of a part or all of the aorta with a consequent reduction of the volume of blood flowing through it. This same thinning of the walls is evident in the cerebral vessels. Survival and capacity for work in such patients depend upon the establishment of collateral circulation through the anastomoses between aorta and subclavian, intercostal, and epigastric arteries. Its diagnosis rests upon symptoms and signs developing along this collateral circulation. These are in the order of their frequency and importance:

1. Hypertension and high pulse pressure in the upper extremities both as compared to normal and to that of the lower extremities.
2. Notching and erosion of the lower rib margins as seen in the x-ray.
3. Pulsations, thrills, bruits, and other sounds along the course of the collateral circulation.
4. Gradually diminishing pulse volume as the terminal arteries of the lower extremities are approached.

J. T., a 20-year-old white secundigravida, para 0, was admitted to the prenatal cardiac clinic in the fifth month of her pregnancy because of hypertension and a cardiac condition noted in the obstetric clinic. Except for occasional headaches, she felt well. She could climb three flights of stairs before becoming dyspneic. There was no orthopnea, precordial pain, palpitation, or edema. She had not been aware of hypertension up to this time. A previous pregnancy had terminated in a spontaneous abortion at two months. There was a history of rheumatic fever at the age of 10 and a recurrence of this disease at 18. After the initial attack, exercise had been restricted because of a heart condition.

Physical examination showed the patient to be free of any distress. Her face was ruddy. Temperature, pulse and respirations were normal. She weighed 130 pounds and was 5 feet 7½ inches tall. Blood pressure was 172/92. Blood Wassermann and urine were negative. Pelvic measurements were normal. The thyroid was symmetrically enlarged to about twice normal size. There was a marked pulsation visible in the suprasternal notch. Lungs were clear. The cardiac apex impulse was palpable in the midclavicular line. On auscultation, the heart sounds were of good quality and there was regular sinus rhythm. A loud, high-pitched systolic murmur was audible in the left third intercostal space and was transmitted upward to the right clavicle. A rasping systolic murmur was heard over the back at the level of the scapula. The aortic second sound was accentuated. The blood pressure of the lower extremities recorded at the popliteal space was 122/90. The femoral pulse on either side did not lag appreciably behind that palpable at the wrists. There was no clubbing of the fingers or toes and no edema.

A 6-foot teleroentgenogram of the chest showed no enlargement of the heart. The pulmonary area was accentuated and the arch of the aorta was small. The lower margins of several ribs on the right side suggested pressure erosion. The transverse diameter of the chest measured 26.7 cm., that of the right heart 4.6 cm. and that of the left 8.6 cm. The total transverse heart diameter was 13.2 cm. The cardiothoracic ratio was 49 per cent. The vascular pedicle measured 5.1 cm. Fluoroscopy confirmed the above findings and showed the aorta to be smaller than normal and somewhat elongated. An electrocardiogram showed only a slight degree of sinus arrhythmia present. Diagnosis of the cardiologist was: Congenital heart disease and rheumatic heart disease, coarctation of the aorta, and normal sinus rhythm, Class I-C.

Because the patient was well along in the second trimester, it was advised that her pregnancy be allowed to continue nearly to term and then be terminated by cesarean section, with sterilization at that time.

Under strict supervision, of both obstetric and prenatal cardiac clinics, she was carried to within three weeks of the expected date of confinement without any untoward signs or symptoms. The blood pressure remained high, ranging between 146/62 and 172/88. Repeated urinalyses were entirely negative.

On admission to the hospital Oct. 15, 1940, the blood pressure in the left arm was 176/106. In the left leg the blood pressure was 110 systolic and diastolic could not be elicited. The fundus contained the breech and was 4 fingers below the xiphoid. The vertex was movable above the brim of the pelvis, back on the left, small parts right. Fetal heart was regular and heard best on the left. By rectal examination, the cervix was soft, thick, and closed; the vertex could barely be reached.

reference to the condition of the mucosa. The amount and character of the discharge were noted. Gram-stained smears were made from the vaginal secretion, the bacteria being subsequently graded according to Schröder.⁵ The pH of the vaginal and cervical regions was determined by the use of the glass electrode, the vagina being tested in three sites: the midvagina, the anterior and posterior fornices.

At each visit, prior to inoculation, and on the seventh and fourteenth days after the last inoculation, the vaginal material was examined for the presence of trichomonads by both wet smear and culture. In cases of *T. tenax* survival, the patients were examined for a much longer period of time. The inoculations were made from the centrifuged concentrates of forty-eight to seventy-two-hour cultures of *T. tenax*. Each patient received three implantations on alternate days.

Three patients were inoculated directly with material from the original source (mouth) of one of the two strains used.

Observations

Group I

These experiments involved the attempts to establish *T. tenax* in the 25 patients free of *T. vaginalis*.

Clinical Status Before Inoculation.—As the result of our questioning, it was found that 10 were symptom free, 12 noticed a slight discharge, while 2 complained of a moderate leucorrhea. One patient, positive for gonococci, suffered from slight burning and itching in addition to a heavy flow.

On examination, it was seen that, of the 14 showing a slight discharge, the discharge was thin and white in 5, mucopurulent in 7, and normally gelatinous in 2. In the 11 others with a mucopurulent discharge, this was moderate in 6 and profuse in 5.

The vaginal and cervical mucosas were normal in 10 patients, slightly reddened in 11, and showed moderate to marked irritation in 4. The external cervical os was normal in 12, slightly eroded in 4, and moderately eroded in 9.

The pH determinations and bacterial types are given in Table I.

TABLE I. PATIENTS FREE OF TRICHOMONAS VAGINALIS

BACTERIAL FLORA		pH		NUMBER OF INOCULATIONS	TOTAL PERIOD OF OBSERVATION (DAYS)	NUMBER OF DAYS POSITIVE FOR <i>T. TENAX</i>
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48- TO 72-HOUR CULTURE <i>T. TENAX</i>		
I	0	----	----	----	----	----
II	5	4.3-5.3	6.0-7.4	3	23-26 (3 patients) 33-91 (2 patients)	None None
III	14	5.0-7.9	6.0-7.6	3	19-28 (10 patients) 45-58 (2 patients) 75-98 (2 patients)	None None None
III	6	4.8-7.9	6.0-7.7	3	26-37-42 19 151 47	2 (3 patients) 3 (1 patient) 7 (1 patient) 18 (1 patient)

The greatest danger of pregnancy, and particularly labor, in these patients is sudden rupture of the thinned-out aorta or cerebral vessels. It is therefore usually advised that pregnancy be avoided by contraceptive devices, or if pregnancy has occurred despite these, interruption be done early. If the patient has been carried to near term, she should be delivered by cesarean section with tubal sterilization.

7101 FOURTH AVENUE
35-15 86TH STREET

IMPLANTATION OF TRICHOMONAS TENAX (BUCCALIS) INTO THE HUMAN VAGINA

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IN PREVIOUS studies it has been shown that the intestinal trichomonad, *Trichomonas hominis*, was unable to establish itself in the human vagina, even under conditions favorable to the growth of *Trichomonas vaginalis*.¹⁻³ Intravaginally implanted *T. hominis* only rarely survived as long as twenty-four hours, and none was found alive at forty-eight hours.⁴

These conclusions leave unsettled the question of buccal contamination as a source of vaginal trichomoniasis. The following observations on the survival of intravaginally implanted *T. tenax (buccalis)* are the result of an attempt to shed further light on this question.

Two groups of experiments were conducted:

1. *Trichomonas tenax* was implanted into 25 trichomonas-free vaginas.
2. *Trichomonas tenax* was implanted into the vagina of 25 women positive for *T. vaginalis*.

Material and Methods

The subjects for these experiments were postnatal volunteers from the Maternity Clinic of the Jefferson Medical College Hospital, 42 of whom were within the three-month postnatal period. The two strains of *T. tenax* used as inoculum were isolated from donors free of all organic disease. No untoward effects were noted when cultures of these strains, with their attendant bacteria, were inoculated intraperitoneally into mice.

On presentation, the patients were carefully examined for abnormalities of the lower genital tract. They were instructed not to douche, to cease all other local treatment, and to return in a week or ten days for inoculations. At each subsequent visit they were questioned concerning local symptoms. The vagina and cervix were examined, with particular

TABLE III. DATA ON PATIENTS SHOWING SURVIVAL OF T. TENAX (BUCCALIS)

PATIENT	SYMPTOMS			SIGNS				pH		GRADE BACT. FLORA	TRICHOMONAS		INOC. AFTER WHICH PATIENT POSITIVE FOR T. TENAX	NUMBER DAYS POSITIVE FOR T. TENAX
	DIS- CHARGE	PRU- RITUS	BURN- ING	AMT. DISCH.	TYPE DISCH.	VAG. INFL.	CERV. EROS.	VAGINA	CERV. OS		VAG.	TENAX		
Before 1. After	-	-	-	+	Thick white	-	-	5.3-5.5	7.0	III	Neg.	Neg.	1st	2
Before 2. After	-	-	-	++	Mucopur.	-	-	5.4-5.7	7.5	III	Neg.	Pos.	1st	2
Before 3. After	+	-	-	+	Thin white	+	+++	5.5-6.2	7.4	III	Neg.	Neg.		
Before 4. After	-	-	-	++	Mucopur.	+	+++	5.6-6.0	7.4	III	Neg.	Pos.		
Before 5. After	+	-	-	++	Mucopur.	-	-	5.4-6.0	7.3	III	Neg.	Neg.	2nd	2
Before 6. After	+	-	-	+	M. P. foamy	+	-	5.4-5.9	6.0	III	Neg.	Pos.		
Before 7. After	++	+	-	+	Thin white	+	-	5.6-5.8	7.0	III	Neg.	Neg.	1st and 2nd	3-2
Before 8. After	++	-	-	++	Thin white	++	-	5.4-5.9	6.5	III	Neg.	Pos.		
Before 9. After	-	-	-	++	Thin white	-	-	4.9-5.4	6.9	III	Neg.	Neg.	3rd	7
Before 10. After	+++	-	-	++	Mucopur.	-	-	5.0-5.7	7.0	III	Neg.	Pos.		
Before 11. After	++	-	-	+++	Mucopur.	+++ (hemor.)	+	7.7-7.9	7.7	III Gc.	Neg.	Neg.	3rd	18
Before 12. After	+	-	-	++	Mucopur.	++	+	7.3-7.8	7.7	III	Neg.	Pos.		
Before 13. After	-	-	-	++	Mucopur.	+	+	5.8-6.4	7.7	III	Pos.	Neg.	1st	2
Before 14. After	+	-	-	++	Thin white	+	+	4.9-6.0	7.7	III	Pos.	Pos.		
Before 15. After	+	+	-	+	Mucopur.	+	+	5.4-6.0	6.8	III	Pos.	Neg.	2nd	2
Before 16. After	+	+	-	+	Thin white	++	+	5.5-6.2	7.0	III	Pos.	Pos.		

Clinical Status Following Inoculation.—In this group, 6 temporary infections with *T. tenax* resulted (Table III). In 2 of the 5 patients with a Grade II flora, symptoms and signs of vaginal irritation increased from slight to moderate, and in one of these the flora shifted to a Grade III. The other 3 Grade II patients, including 2 with normal cervical and vaginal mucus, showed no significant changes. Of the 5 with a normal vaginal and cervical mucus, there was no change in 2, with a shift from slight to moderate irritation in 3.

The 9 remaining patients showed no significant alterations in symptoms or signs. The occurrence of mild vaginal inflammation was attributed to the metabolic products of the bacteria and flagellates in the inocula.

Group II

In this group, *T. tenax* was transferred to an environment suitable to the growth of trichomonads, as indicated by the presence of *T. vaginalis* in the 25 vaginas inoculated.

Clinical Status Before Inoculation.—As reported by the patients, *T. vaginalis* caused no discomfort in 5, while 18 complained of a slight to moderate discharge, and 2 of a heavy flow accompanied by burning sensations about the genitals, and a slight pruritus.

On examination, 10 showed a thin, white discharge, 15 a mucopurulent one. Only six displayed the foamy type of secretion, described as characteristic. One had moniliasis.

Irritation of the vaginal and cervical mucus was observed in 21 patients, 6 of whom showed "flea bitten" areas. The vagina and cervix were normal in 4, slightly to moderately irritated in 14, and markedly inflamed in 7. In 4 patients who complained only of a slight discharge, the vaginal picture was that described as typical for *T. vaginalis*-vagin-itis, the "strawberry" vagina. The cervical erosion noted in 8 patients was slight in 5, moderate in 3.

The pH and bacterial findings are recorded in Table II.

TABLE II. PATIENTS POSITIVE FOR TRICHOMONAS VAGINALIS

BACTERIAL FLORA		pH		NUMBER OF INOCULATIONS	TOTAL PERIOD OF OBSERVATION (DAYS)	NUMBER OF DAYS POSITIVE FOR T. TENAX
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48- TO 72-HOUR CULTURE T. TENAX		
I	0	----	----	----	----	----
II	1	4.2-5.6	6.5-7.0	3	30 (1 patient)	None
III	22	4.9-7.3	6.2-8.0	3	19-26 (12 patients)	None
					30-35 (5 patients)	None
					47-67 (3 patients)	None
					82-89 (2 patients)	None
III	2	4.9-6.4	7.0-7.7	3	61-89	2 (both patients)

Clinical Status Following Inoculation.—Despite the suitability of the environment, as indicated by the presence of *T. vaginalis*, only 2 cases of temporary survival of implanted *T. tenax* occurred in this group, in contrast to the 6 survivals in the 25 trichomonas-free vaginas (Table I). There were no significant changes in signs or symptoms in this group as a result of the inoculations.

monas in man and, Is vaginal infection acquired as a result of contamination by material from either the rectum or the mouth?

Because of the fact that *T. hominis* and *T. tenax* display decidedly different abilities to survive in the human vagina, and because neither is able to produce a permanent intravaginal infection, either in the presence or absence of *T. vaginalis*, we conclude that not only are the mouth and intestine not sources of vaginal trichomonad infection, but that each of these three sites is occupied by a distinct species of trichomonas.

We are grateful to Dr. Norris W. Vaux and Dr. D. H. Wenrich for their interest and helpful advice.

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ACTINOMYCOSIS OF THE OVARY

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JOLIET, ILL.

(From the Department of Pathology and the Medical Service of
the St. Joseph's Hospital)

IN A review of the literature, Cornell¹ found 71 published cases of actinomycosis of the internal female genitals. Of these, 7 appeared in the American literature, 6 in the English and the remaining in foreign publications. This disease of the internal female sex organs is being reported with increasing frequency in the last few years and, in the majority of the cases, the lesions are found to affect the uterine adnexa. Most of the authors emphasize the great resistance of the uterus to the infection, stating that if the uterus does become involved it is due to the extension of the process from the parametrium (Nurnberger,² Daniel and Mavrodin,³ Cornell,¹ and others). The actinomycosis of the adnexa is usually secondary to an infection of the intestine, particularly of the cecum or appendix. Blasek⁴ has pointed out that actinomycotic infection may progress while the primary lesion in the intestine heals. Daniel and Mavrodin³ refer to the external genitals as a possible port of entrance of the infection.

Occasionally, cases are described which suggest that the fungus may directly infect the internal female genitals, the primary lesion being located in the uterus. Such a portal of entrance is suggested in the following case:

The patient was first seen by one of us (Dr. Fahrner) in August, 1936, when she was 32 years of age. At this time, this white female of Polish

*In active military service.

Patients Showing Survival of Culture Trichomonas tenax (buccalis).—There was a total of 8 patients (16.0 per cent) who showed at least a forty-eight-hour survival of implanted *T. tenax*. Five were positive at the end of the forty-eight-hour period only; 1 was positive at seventy-two hours, when another implantation was made, and she was still positive at one hundred twenty hours; while 2 were still showing *T. tenax* on the seventh and eighteenth days, respectively, after the last inoculation. It would seem that in these last two patients intravaginal multiplication of the oral flagellate had definitely occurred.

In 3 of the 6 successful *T. vaginalis*-free cases (Patients 1, 4, and 6), *T. tenax* was present in sufficient numbers to be noted in the routine wet smear. The other three were diagnosed by culture only.

In these *T. tenax*-positive patients, the symptoms and signs did not vary significantly from those present prior to implantation (Table III). Two patients (2 and 3) complained of a slight discharge, and in 3 (Patients 1, 2, and 4) there was a mild increase in vaginal secretion. Three (Patients 3, 4, and 8) also presented a temporary increase in mucosal irritation.

Patients Receiving Direct Inoculation of T. tenax.—Three patients were inoculated once each with material directly from a positive mouth. No intravaginal survival of *T. tenax* was noted. The brevity of this phase of the problem is excused only on the basis of the intervention of military service.

Summary

1. Twenty-five *T. vaginalis*-free patients were inoculated intravaginally with *T. tenax (buccalis)* resulting in 6 temporary infections. There were 3 survival periods of two days each, and one each of three, seven, and eighteen days.

2. Twenty-five *T. vaginalis*-positive patients were inoculated intravaginally with *T. tenax*, resulting in 2 temporary infections. There were 2 survival periods of two days each.

3. *T. tenax* appeared to effect a temporary establishment in one patient, surviving for at least eighteen days.

4. The temporary residency of culture *T. tenax* and its associated bacteria caused little or no increase in local symptoms and signs.

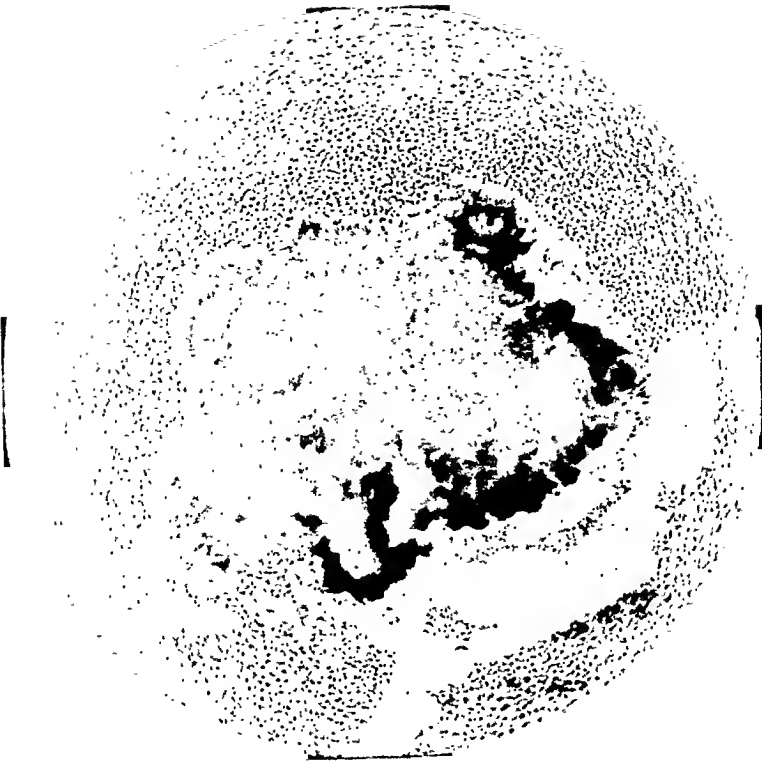
5. Intravaginal survival of *T. tenax* was more infrequent and of less duration in those patients positive for *T. vaginalis*.

6. Three brief experiments involving the direct transfer of *T. tenax* from mouth to vagina gave negative results.

7. From the evidence presented, it is concluded that the mouth is not a source of vaginal trichomoniasis, and that the two sites are inhabited by two distinct species of trichomonas.

Conclusions

The experiments just reported on the intravaginal implantation of *Trichomonas tenax*, as well as the similar ones previously reported involving inoculations of *T. hominis*, were performed in an attempt to shed light on the questions: Is there more than one species of tricho-



A.



B.

Fig. 1.—Photomicrograph of bacterial clouds seen in the ovary. Note the club-shaped organisms at the periphery. A, $\times 200$. B, $\times 410$.

descent had some pleurisy on the left side. By October she was discharged as cured. She was not seen again until December, 1938. At this time she complained of pain in the lower pelvis, and extreme weakness which had been present for six weeks. The red blood count was 3,680,000; hemoglobin, 53 per cent; white blood count, 22,000; with 70 per cent polymorphonuclear leucocytes, and 2 per cent eosinophiles. There was a marked anisocytosis and poikilocytosis. She was treated for the anemia and felt better. In February, 1939, she was seen again. At this time her red blood count was 3,504,000; hemoglobin, 48 per cent and white blood count, 14,000. Examination revealed a pelvic mass in the left broad ligament, and the patient was advised to enter the hospital.

Bleeding from the rectum following stools was also present. No gross hemorrhoids were visible. In March she entered the hospital. On questioning, it was learned that she had irregular spells of vomiting, occasional chills, and fever and pain on defecation. She had had an appendectomy in 1927, and several pregnancies but always miscarried. An X-ray study suggested an annular defect involving the entire rectal ampulla which was interpreted as a carcinoma. Because of the marked anemia she was given three blood transfusions in preparation for operation. A laparotomy was performed under nitrous oxide and ether anesthesia. The organs in the pelvis were bound down to form a "frozen pelvis." The sigmoid colon was adherent to the pelvic mass, but no mass was palpable in its lumen. The rectum on palpation revealed no evidence of any unusual thickening of its wall. The left Fallopian tube was adherent to the ovary to form a mass which was dissected free, and removed. The specimen for examination consisted of a Fallopian tube attached to the ovary. The ovary measured 5 by 4 by 3 cm. On sectioning it contained pus filled, irregular cavities. One of these cavities fused with the tortuous Fallopian tube, forming a tuboovarian abscess. There was submitted also a separated portion of tissue which was ovoid and measured 3.5 by 3 by 3 cm. This was soft, elastic in consistency, and on the surface, irregular. On sectioning it was purple red and mottled with areas of lighter yellow. On pressure yellow, purulent material was expressed. Sections taken through the ovarian portion of the specimen revealed a marked infiltration with round cells and neutrophils. Sections from the irregular mass showed ovarian stroma with an inflammatory exudate similar to that described above and, in addition, clouds of hyalinelike staining material, at the periphery of which were club-shaped structures. The histologic picture was suggestive of the ray fungus (Fig. 14). No cultures were obtainable since the specimen was fixed in formaldehyde. The postoperative course was stormy. The patient was given 12 blood transfusions and treated symptomatically. She made a gradual improvement and an x-ray of the pelvis showed a foreign metallic body, resembling a hairpin, apparently lodged either within the cervix or in the uterine cavity (Fig. 2). Questioning of the patient yielded the information that she recalled having used a hairpin for the purpose of inducing an abortion. She refused to give any further details.

After a stay in the hospital of thirty-two days she was discharged in fair condition. She reappeared in June because of a draining wound, and anemia. She was given several blood transfusions. The blood count showed hemoglobin 44 per cent (6.4 Gm.); and red blood count 2,410,000. This count was elevated to 56 per cent (8.0 Gm.), and red blood count, 3,050,000.

break in the continuity of the tissues. Giordano⁷ reported a case in a woman aged 64 years, who formerly fed the chickens grain. Her uterus was prolapsed, and on the posterior lip of the vaginal portion of the cervix there was a small indurated area. The external uterine orifice was half open, and the cervical canal contained a thick, cloudy fluid in which the characteristic sulphur bodies were suspended. Vaginal hysterectomy was followed by complete recovery. Giordano suggests that the spores of the fungus were present in the grain used for feeding the chickens, and that they might have settled on the eroded and prolapsed cervix of the uterus. In two instances the actinomycosis of the uterus followed an instrumental abortion (Haselhorst,⁸ and Junghans⁹). In Haselhorst's case, a fistulous tract extended from near the internal uterine orifice into the left parametrium which was the site of a sclerosing, suppurative inflammation involving the left tube, the sacral bone, and the fifth lumbar vertebra. Junghans' case showed an instrumental perforation in the anterior wall of the vagina from which the actinomycotic infection seemed to have taken origin. In the cases described by Barth¹⁰ and Tietze,¹¹ the infection was traced to ulcerative lesions caused by intrauterine, contraceptive pessaries. The mode of infection in the cases of Mitra¹² and Christeller¹³ is obscure. Coventry¹⁴ reports a case in a woman 20 years of age in whom an actinomycotic infection of the ovary was found but no source of the primary was established.

In our case the mode of infection suggests itself to be the introduction of the hairpin into the uterus. The patient lives in a city of about 45,000 which is surrounded by a farming community. Attempts to elicit information from the patient as to the source of the hairpin, or whether she was on a farm at the time, failed. Although the roentgenologic evidence pointed to a lesion within the intestine none was found at operation, and her obstructive symptoms were most likely due to pressure by the granuloma from the outside. We have been unable to determine the extent of involvement of the uterus since the patient is in no condition, at the present time, for further surgical manipulation. It is hoped, however, that further information can be obtained.

Summary

An actinomycotic involvement of the left ovary was found at operation. The portal of entrance was probably the uterus. A foreign body seen on the x-ray resembled a hairpin in the uterus. This was substantiated by the patient.

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The patient left the hospital and went to another institution where cultures from the abdominal wound revealed organisms which showed cultural characteristics of actinomyceetes. Cultures from the stool did not show these organisms. The patient re-entered the hospital in December with symptoms of pain in the left upper quadrant associated with obstructive symptoms. A colostomy was performed. She was given supportive measures and symptomatic treatment. In February, 1940, the colostomy was closed and in the month of March the patient was discharged much improved. An x-ray at this time still revealed the foreign body in the uterus.



Fig. 2.—X-ray showing foreign body in the uterus.

Discussion

Some of the cases of actinomyces were so-called purely on the identification of the granules by their morphology, since no cultures were made as in the case of Jaffé.⁵ The case reported by Jaffé was one of a cyst of the cervix uteri in which routine microscopic examination revealed the club-shaped thickenings of the free ends of the mycelia. In all the cases of actinomyces of the uterus described in the literature the diagnosis was based upon the demonstration of the characteristic bodies either in sections or smears but not by culture.

Actinophytic evolution forms of certain bacteria, notably staphylococci (botryomyces), can be confused with actinomyces. In chronic suppurative osteomyelitis, the staphylococci form occasionally compact clumps which are surrounded by a homogeneous shell. Berger, Vallee, and Vezina⁶ have described a staphylococcal actinophytosis of the vulva. It is, however, only under low-power magnification that the staphylococcal granules can be mistaken for actinomyces, since the finer morphology is different, the former being composed of cocci, the latter of branched filaments.

Varied explanations are given to account for the entrance of actinomyces into the uterus. In order to infect, the actinomyces must find a

Radium Therapy in Benign Uterine Bleeding. A. J. Rongy, M.D., and A. D. Seley, M.D., New York, N. Y. (For original article, see page 390.)

Urinary Incontinence in Women. Virgil S. Counseller, M.D., Rochester, Minn. (For original article, see page 479.)

Complications of Abdominal Surgery and Their Management. W. Wayne Babcock, M.D., Philadelphia, Pa.

The Involutional Phase of the Menstrual Cycle (Climacteric). Robert A. Ross, M.D., Durham, N. C. (For original article, see page 497.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 1, 1942

The following paper was presented:

Hormonal and Other Physiological Studies on the Ureter During Pregnancy. John Mason Hundley, Jr., M.D., Baltimore, Md. (by invitation).

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 6, 1942

The following paper was presented:

Résumé of Cardiac Disease in Pregnancy for a Five-Year Period. Drs. Thomas R. Turino and J. Thornton Wallace. (For original article, see page 526.)

MEETING OF NOVEMBER 6, 1942

The following papers were presented:

The Management of Ovarian Tumors in Elderly Women. Dr. Joseph W. Goldsmith, Jr. (For original article, see page 518.)

Pathology of Postmenopausal Bleeding. Dr. Ralph M. Schwartz. (For original article, see page 522.)

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

*FIFTY-FIFTH ANNUAL MEETING, HOT SPRINGS, VA.,
SEPTEMBER 10 TO 12, 1942*

The following papers were presented:

- President's Address—Factors Influencing the Geographic Distribution of the Obstetrician-Gynecologist. Grandison D. Royston, M.D., St. Louis, Mo. (For original article, see page 365.)
- Group Incidence of Hypertensive-Albuminuric Pregnancy Under the New Classification. Foster S. Kellogg, M.D., Boston, Mass. (To be included in the April issue.)
- Modern Trends in the Management of the Third Stage of Labor. Richard Paddock, M.D., St. Louis, Mo.
- Medical Complications of Pregnancy and Labor. Louis H. Douglass, M.D., Baltimore, Md. (by invitation).
- Clinical Differential Demonstration of Uterine and Tubal Contractions by Kymographic Uterotubal Insufflation. I. C. Rubin, M.D., New York, N. Y. (For original article, see page 419.)
- The Glycogen Index in the Menopause. Harold C. Mack, M.D., Detroit, Mich. (For original article, see page 402.)
- Comments Upon Certain Phases of Surgical Technique. Edward A. Schumann, M.D., Philadelphia, Pa. (by invitation).
- Hydatidiform Mole and Associated Tumors of the Chorion. Tiffany J. Williams, M.D., University, Va. (by invitation). (For original article, see page 432.)
- Post-Partum Observation of Pelvic Tissue Damage. Harold L. Gainey, M.D., Kansas City, Mo. (by invitation). (For original article, see page 457.)
- Sarcoma of the Uterus. Clyde L. Randall, M.D. Buffalo, N. Y. (by invitation). (For original article, see page 445.)
- A Report of the Cesarean Sections Done at the Philadelphia Lying-in-Pennsylvania Hospital. Roy W. Mohler, M.D., Philadelphia, Pa. (by invitation). (For original article, see page 466.)
- Factitial Proctitis. Lawrence M. Randall, M.D., and L. A. Buie, M.D., Rochester, Minn. (For original article, see page 505.)
- Posterior Vaginal Enterocoele. Louis E. Phaneuf, M.D., Boston, Mass. (For original article, see page 490.)
- The Effect of Preoperative Irradiation on Adenocarcinoma of the Uterus. Herbert E. Schmitz, M.D., John F. Sheehan, M.D., and Janet Towne, M.D., Chicago, Ill. (For original article, see page 377.)

the mortality was 0 per cent. The authors state that in infected cases Mikulicz' drainage should be particularly useful when associated with a method for protecting the peritoneal cavity.

J. P. GREENHILL

Johnston, H. W.: The Termination of Pregnancy Before the Period of Viability by Abdominal Hysterotomy Through the Lower Uterine Segment, Canadian M. A. J. 43: 552, 1940.

Circumstances occur when pregnancy has to be terminated before the fetus is viable. Before the end of the third month abortion may be carried out by the usual method of dilating and curetting the uterus. From the commencement of the fourth month and afterwards termination of a pregnancy by vaginal manipulation is accomplished with difficulty and may be dangerous. The method described by H. W. Johnston (Toronto) is an operation that may be adopted when the pregnancy has advanced to the fourth month and must be terminated, or when sterilization is advisable at the same time the uterus is emptied.

Abdominal evacuation of the uterus may be carried out by classical hysterotomy or by an incision through the lower segment. The latter method has one distinct advantage. Uterine contractions are not as powerful or as prolonged in the early months of pregnancy as they are at term, so that a mild postoperative leakage is of frequent occurrence. When the incision is through the peritoneal coat of the uterus this oozing is intraperitoneal. Loops of intestine may become adherent to the clotted area and give rise to intestinal obstruction. The lower segment approach reduces this to a minimum, as the incision in the uterus is extraperitoneal.

A series of descriptive drawings illustrating the steps of the operation is presented by the author.

J. P. GREENHILL

Payne, Waverly R., and Bland, Harvey G.: Cesarean Section With Special Reference to Lower Segment Operations. An Analysis of 110 Consecutive Cases, South. M. J. 34: 689, 1941.

This study covers a ten-year period, from Jan. 1, 1930, to Oct. 1, 1940. During that time 1,455 women were delivered. Of this group, 110 were delivered by cesarean section, an incidence of 7.56 per cent, which is much higher than that recorded by some of the larger clinics. There were no maternal deaths following cesarean section. There were 114 babies born alive, including three sets of twins.

The lower segment operation was employed 89 times. Preference has been shown the transverse incision, but in some cases presenting a deep pelvis, making the exposure difficult, the low longitudinal or laparotrachelotomy of DeLee has been done. The lower segment operations, having proved safer in potentially infected cases, have been the choice in many clean or elective cases. In this series the high classical was not done, and the low classical only in elective cases with unruptured membranes or in placenta previa.

The authors have used general anesthesia most frequently. They believe that spinal anesthesia, in dosage limited to 100 mg. of procaine hydrochloride, is a very useful agent in certain types of cases, especially the severe toxemias or patients with acute respiratory infections.

J. P. GREENHILL

Schmelzer, F.-J.: Racio-Political Significance of Cesarean Section—A Study of Fertility Subsequent to Section, Zentralbl. f. Gynäk. 64: 1354, 1940.

The author studied 114 patients who had been delivered by cesarean section. Further pregnancies occurred in 79 per cent. In 68 per cent of these, conception occurred within the first three years after the operation.

Department of Reviews and Abstracts

Selected Abstracts

Cesarean Section

Hennessey, J. P.: Cesarean Section; a Review of 316 Cases, North Carolina M. J. 3: 217, 1942.

During the thirteen years from 1928 to 1941 inclusive, 316 cesarean sections were performed at St. Ann's Maternity Hospital (New York), an incidence of 3.44 per cent. Although the ward and private deliveries were approximately equal, the incidence of section was higher on the private service. Over half of the sections were performed because of contracted pelvis. Previous stillbirth and difficult delivery is the next most common indication, followed by elderly primiparity. There were 88 patients with one or more previous sections. Two of these ruptured their uteri during labor, and one died following repair of the rent. There were 287 classical sections, 21 low flap, 4 Latzko, 3 Porro, and 1 Waters. The stillbirth and neonatal death rate was 4.52 per cent, gross maternal mortality 2.53 per cent. The state of the membranes did not appear to affect the mortality or morbidity.

L. M. HELLMAN

Sala, Silvestre L., and Ferrari, Roberto A.: Mikulicz's Drainage Following Cesarean or Infected Cases, Arch. de la Clinica Obst. y Ginec. 1: 186, 1942.

The authors present the results obtained in 43 cesarean sections performed on infected cases using Mikulicz's drainage. In 36 cases the regular drain was used and in the other 7 an ordinary gauze drain. The drain was left in place for two to thirteen days, average time five and one-half days. Postoperatively, 23 cases were febrile, 18 subfebrile and 2 were afebrile. Secondary healing occurred spontaneously in 37 cases; in 4 cases new sutures were placed to approximate the margins of the incision. Primary healing occurred in two cases. No complications other than those inherent in the method were observed. There were no eviscerations or subsequent hernias which, according to some reports, frequently occur. These accidents, the authors believe, are due to premature withdrawal of the drain and can be avoided by leaving it in situ for at least five to six days, and in certain cases by using wire for the approximation sutures. Intestinal or urinary fistulas and intestinal obstruction also were not observed and, in the authors' opinion, these accidents can be obviated by using the Cofferdam-Mikulicz drain proposed by Palazzo, the rubber covering of which separates the viscera from the gauze, preventing their adherence.

Three of the 43 patients died, excluding one patient who died of influenza and emboli at 115 days; the mortality due to peritonitis was 5.26 per cent. This is considerably lower than the 12.5 to 17 per cent mortality reported in other studies. In these studies the authors discovered that fatal peritonitis occurred in those cases where cesarean sections were performed without special protection of the peritoneal cavity. In their own series where such precaution (method of Leon) was observed,

ovarian cysts are adenomatous, simple serous, follicular, lutein, dermoid, hydatid, Krukenberg tumor and carcinomatous.

An ovarian cyst during pregnancy can be diagnosed in most cases from the characters of the tumor; if it is infected or its pedicle is twisted, it is painful on palpation or spontaneously. The diagnosis of pregnancy should not offer any difficulties. Usually, the diagnosis of pregnancy complicated by cysts is easy during the first months, but difficulties arise at or near term when the pregnancy hides a small or average-sized cyst which cannot be reached by palpation, or when a cyst nearly fills the abdomen and hides an incipient pregnancy in a retroflexed or raised uterus. The biologic tests and roentgen examination must then be used. The differential diagnosis includes ascites, extrauterine pregnancy, and acute hydramnios.

Ovarian cysts cause sterility in from 16 to 34 per cent of the cases. They may not have any effect on the evolution of pregnancy, but they cause extrauterine pregnancy, compression and torsion of the pregnant uterus, abortion (from 7.5 to 17 per cent), premature birth, prolapse and edema of the cervix. The effects of pregnancy on cysts include compression, torsion, necrosis, suppuration, rupture, and resorption.

The treatment of ovarian cyst during pregnancy should be surgical. Some authors prefer operating during the first half, others during the second half and others at any time of pregnancy. It is best to adhere to the following rules. Small cysts causing no disturbance are left alone. Cysts, the size of a mandarine or a fetal head, must be extirpated, but only after completion of the fourth month of pregnancy if they cause no important disturbance. Cysts of average or large size, adhering to, compressing or imprisoning the uterus in the small pelvis, and cysts which cause great disturbances are operated upon immediately. When the indication for operation arises at the end of pregnancy, the advisability of simultaneous cesarean section must be considered, because the scar is not likely to resist rupture if labor occurs a few days after the operation. However, the size of the fetal head, primiparity or multiparity, the condition of the patient, etc., should be taken into account, and in special cases, particularly in large adherent cysts, puncture if labor is near, or induction of labor by chemical or biologic means may be attempted.

A small or average sized cyst during labor may not cause any trouble and remain unrecognized. In case of dystocia, treatment will vary. The cyst may rupture spontaneously, eliminating the dystocia. Otherwise, the choice lies between three methods: Displacement, or manual reduction, must always be tried no matter how far advanced the labor is; strict asepsis, general anesthesia, and avoidance of force are essential. Puncture may be used in special cases, but not as a procedure of choice, provided that the cyst is easily accessible, the patient's condition is good, the birth canal and the cyst are not infected and displacement has failed. After puncture and termination of labor, if no complications are expected, the patient is simply kept under careful observation during the puerperium; if the birth canal or the cyst was infected or only suspected, the cyst must be extirpated immediately after delivery. Extirpation with or without cesarean section or cesarean section with or without extirpation is the last recourse when displacement has failed and puncture is impossible.

Ovarian cysts during the puerperium may remain unrecognized because of their size. Therefore, no patient should be discharged before a complete gynecologic examination is made. The most serious accident which may occur is infection and suppuration of the cyst. Infection may be direct, or through the lymphatic or circulatory route. Torsion is second in importance and frequency; sudden acute pain, irradiating to the lumbar region and the thighs, vomiting, etc., impose the necessity of internal examination to differentiate the uterus from the cyst which is sensitive to palpation. Any ovarian cyst with a pedicle in a normal puerperium must be removed by the abdominal route. If the cyst is only slightly movable or intra-

Number of patients subsequently pregnant	83
Number of pregnancies	158
Of these 26 terminated in abortion	
45 terminated in section	
87 delivered per vaginam	
24 patients had 2 sections each	
9 patients had 3 sections each	

Of 24 patients not having subsequent pregnancy 13 did not desire pregnancy. The author concludes that the number of normal deliveries preceding the pregnancy which ended with cesarean section has an influence upon further fertility. In a comparison of the number of pregnancies for equal years of marriage, those having the operation showed a lower total fertility than those who had no operative deliveries. However those patients subjected to operation at the first pregnancy had an average of 1.46 children subsequently as against 1.0 children brought forth by those having the operation at a second or later pregnancy. Schmelzer feels that in the interest of the child as well as with a view to future parity, cesarean section should be resorted to in most cases of dystocia as well as in placenta previa.

R. J. WEISSMAN

Burger, K.: Observations on Cesarean Section, *Zentralbl. f. Gynäk.* 64: 1361, 1940.

Burger uses wet packs wrung out of antiseptic (rivanol) solution surrounding the uterus before incising it. In cases presumably infected, an intrauterine antiseptic soaked pack is left for forty-eight hours.

R. J. WEISSMAN

Labor

Schaffer, Bernado, and Rodriguez, Nicanor: Episiorrhaphy: Technic of Dr. J. B. Gonzales, *Bol. Soc. de obst. y ginec. de Buenos Aires* 20: 843, 1941.

The authors used the Gonzales technique in seven episiotomies and in two first, one second and two third degree perineal tears, with immediate satisfactory results. Repair is simple in episiotomy and becomes more difficult in episiotomy with secondary tear or in primary tears. The tissues possess great powers of healing and resistance to infection; when infection occurs, it usually comes from the uterus. Good local or regional anesthesia, proper surgical conduct, and perfect identification of the corresponding anatomic points on each side of the wound are indispensable. Tears with necrotic tissue or pockets are treated in the usual surgical manner. Lesions of the terminal portion of the rectum are repaired before the perineal lesion itself. The Gonzales technique is simply a modernization of the principles applied before antisepsis and modern suture materials were used. Hemostasis should be sufficient but not pushed to extremes. Heavy linen or silk sutures are indicated, because they favor better coaptation, cause less tension in the tissue and insure against cutting through them. Renewal of dressings will depend on local conditions, such as lochial discharge. In some cases, a permanent catheter in the bladder is advisable to protect the wound. In rectal lesions the patient is kept constipated to give the part the rest necessary for healing.

J. P. GREENHILL.

Gavioli, Richardo L.: Ovarian Cysts and Puerperality. Clinical Study, *Bol. Soc. de obst. y ginec. de Buenos Aires* 20: 771, 1941.

The incidence of ovarian cysts in pregnancy varies with statistics from 0.15 to 6.27 per cent; in Gavioli's experience it was 1 in 1,280. The most frequent types of

In his discussion and conclusion Makepeace emphasizes that home-delivery service, attached to medical schools, should be conducted so that the standards of medical care are on a level with those maintained in the hospital connected with the medical school and the area, covered by the service, should be close to a hospital having specialized obstetric service.

Although Makepeace states that home-delivery service will necessarily have to be included in periods of medical school training he agrees with Norman F. Miller, "obviously the ultimate objective of every community should be to have all maternity patients delivered in hospitals maintaining approved standards for the care of maternity patients, by—or under the supervision of—physicians trained in obstetrics."

CLAIR E. FOLSOME.

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Wednesday, May 19, through Tuesday, May 25, 1943. The Hotel Schenley in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for reexamination in Part II must make written application to the Secretary's Office not later than April 15, 1943.

The Pittsburgh Obstetrical and Gynecological Society will hold a subscription dinner meeting at the Hotel Schenley, on Saturday evening, May 22, 1943, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary of the Society, at 121 University Place, Pittsburgh, Pa. An interesting program is being provided.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board. Applications are now being received for the 1944 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

ligamentous, extirpation may be referred until the patient has completely recovered and involution of the genital organs has taken place.

J. P. GREENHILL.

Zoller, C. M.: Labor and Puerperium in Overweight Women, *Monatsh. f. Geburtsh. u. Gynäk.* 113: 25, 1942.

The author investigated a series of 600 pregnant women who were overweight. He found that such women have a tendency to develop kidney trouble, pre-eclampsia, and eclampsia. A large proportion have premature rupture of the membranes. Because of the difficulties in labor, operative interference is more necessary than usual. Likewise, hemorrhages in the third stage are common. The puerperium is frequently febrile. The author warns that more careful observation of fat women is necessary. The diet of these women should be carefully controlled.

J. P. GREENHILL.

Wilson, Karl M.: Obstetric Problems Arising From Excessive Size of the Infant, *New York J. Med.* 42: 883, 1942.

A series of 495 infants whose birth weight was 4,000 Gm. or over is presented. There were 82.3 per cent of the labors terminated spontaneously, operative interference was necessary in 17.7 per cent, while labor was induced in 5.6 per cent. When dystocia occurs in connection with the baby of excessive size, the difficulty is seldom due to excessive size of the head but rather is the result of shoulder dystocia. The risk to the baby increases greatly when the weight exceeds 4,500 Gm. Thus, in this series, the fetal mortality in infants weighing 4,000 to 4,499 Gm. was 3.2 per cent, in those weighing 4,500 to 4,999 Gm. it was 4.8 per cent, while the mortality figure reached 36.0 per cent in infants weighing 5,000 to 5,499 Gm. and was 100 per cent in three infants weighing over 5,500 Gm. Birth injuries were rather more frequent than usual in the series, such injuries including six cases of Erb's palsy and three fractured clavicles. Suggestions for management of this situation include dietary restriction of fat-forming foods taken by the mother during the last weeks of pregnancy, induction of labor when a child of unusual size is discovered in the latter part of pregnancy, and cesarean section in properly selected cases, especially if the child appears to be over 5,500 Gm.

Makepeace, A. W.: The Home Delivery Service, *The Child* 7: 36, 1942.

Makepeace, now Consultant in Obstetrics, North Carolina State Board of Health and Professor of Obstetrics, School of Public Health, North Carolina, was engaged by the Children's Bureau, to survey and study the home-delivery services in 15 medical schools for white students. Most of the schools, listed by alphabetical legend, were in the southern part of the United States.

In all 15 schools visited, the students, prior to assignment to the home-delivery service, received instruction in basic normal obstetrics but in only 10 of the 15 schools was the home investigated to determine its suitability for delivery. Transportation to the home was a student problem in all but 4 of the 15 institutions. Student responsibility, during labor and delivery, varied from zero (3 schools) to 100 per cent (2 schools). The caliber of medical care varied from mediocre to adequate. (Detailed charts demonstrate these facts excellently.)

The nursing care in the home-delivery service was found to be variable. A nurse was required to be present in only 7 of the 15 schools conducting home-delivery service. Morbidity and mortality records were available in only 8 of the 15 institutions visited.

content of the blood,^{19, 36} a reduction of red cell count, hemoglobin, hematocrit^{13, 15} and plasma proteins.^{39, 40} This increase is said to reach a maximum of 25 per cent or more at the ninth lunar month after which some diminution occurs before labor.^{17, 50} The usual proportion of available extracellular water in pregnant women weighing less than 120 pounds has been found to range from 33 to 37 per cent of the total body weight, as compared to an average of twenty to 26 per cent in nonpregnant women.⁸

The retention of sodium parallels that of water, for a consistently positive balance, for this ion has been shown to exist during the latter months of pregnancy.^{11, 21, 48, 49} A part of the positive sodium balance can be attributed to the needs of the developing maternal and fetal tissues, but there is in addition an altered capacity of the pregnant woman to eliminate sodium. This is shown in the retention of relatively large proportions of administered sodium chloride,^{34, 41} and in the delayed elimination of measured quantities of ingested water.^{30, 35}

With parturition changes in these relationships set in. During labor and immediately afterwards, the blood becomes more concentrated.^{1, 17} This is in part due to blood loss, partly to the effects of muscular effort and dehydration and perhaps in part to a redistribution of water as a result of the disappearance of the placental circulation. This period of blood concentration is of short duration, however, for within forty-eight hours the plasma volume again rises^{1, 13, 39} and immediately thereafter diuresis commences. Large quantities of sodium appear in the urine during the next few days⁴⁸ and there is a considerable loss of available extracellular water.⁸ The secondary expansion in the plasma volume after delivery may be attributed to the return of the excessive quantities of interstitial fluid to the vascular stream. This in turn leads to the diuresis of the early puerperium.

In the specific toxemias of pregnancy, pre-eclampsia and eclampsia, somewhat different conditions obtain. Here the edema, gain in weight and water retention are greater. The capacity rapidly to eliminate excessive sodium is apparently further reduced and administration of sodium chloride may precipitate a considerable exacerbation of symptoms.^{26, 27, 46} Water diuresis is also further delayed.³⁵ The blood in pre-eclampsia does not partake in the fluid increase, however, for now, as numerous observers have pointed out, there is a relative concentration of the blood as indicated by increase in cell volume, hemoglobin, proteins, and certain other constituents of the blood.^{13, 42, 44} Albers¹ has recently reported a greatly reduced plasma volume in "hydrops gravidarum." Blood dilution occurs with clinical improvement during the course of the toxemia and follows rapidly the death of the fetus or parturition.⁴² The fact that in toxemia there is increased water in the tissues and a relative hemoconcentration suggests that the water retention is due to a barrier between tissue and blood stream and not between blood stream and kidney.

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Original Communications

THE RELATIONSHIP OF THE ESTROGENS AND PROGESTERONE TO THE EDEMA OF NORMAL AND TOXEMIC PREGNANCY*

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THE tendency to retain water in the tissues is a well-recognized characteristic of normal pregnancy. In the specific toxemias, a further decrease in the ability to eliminate water results as a rule in greater degrees of edema. Following both normal and toxemic pregnancy, the excess water is rapidly eliminated during the first few days of the puerperium.

In a previous report, we submitted evidence to show that the retention of sodium and water during pregnancy was due to the estrogenic material produced by the placenta and its loss during the puerperium to the disappearance of the estrogens. In the present study, the relationship has been further investigated by the administration of large doses of these substances during pregnancy and the puerperium.

Introduction

The retention of water in normal pregnancy is indicated by the degree of weight gain, by the frequent slight edema of the lower extremities, by an increase in the volume of plasma^{1, 17, 31} and of extracellular water.⁶ The rise in plasma volume is manifested by an increased water

*This study was carried out with the aid of a grant from the Commonwealth Fund.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. EFFECT OF ESTRADIOL BENZOATE ON SODIUM BALANCE IN NORMAL PREGNANCY AND PUERPERIUM (CASE 6)

CLINICAL					SODIUM BALANCE					TREATMENT	
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY		DAILY BALANCE
23		126½	0	990	2.45	0.58	0.015		0.04	-0.38	30,000 R. U. 90,000 R. U. 60,000 R. U.
22		125	0	2,180	2.45	2.81	0.015			+1.70	
21		124	0	1,270	2.45	0.73	0.015			+0.77	
20		124	0	1,655	2.45	1.62	0.063			+1.20	
19	100/70	123½	0	1,635	2.30	1.04	0.063		0.06	+0.79	
18	106/68	124½	0	1,530	2.30	1.39	0.063		0.08	+0.73	
17	108/70	124	0	2,169	2.30	1.51	0.063		0.06	+1.27	
16	106/70	124	0	1,175	2.32	0.91	0.063		0.06	+0.49	
15	102/68	124¼	0	1,680	2.32	1.71	0.063			+0.19	
14		124	0	2,245	2.32	2.11	0.020			-0.36	
13	102/78	125	0	1,205	1.86	2.20	0.020			+0.83	
12	92/64	125¼	0	1,425	1.86	1.01	0.020		0.06	+1.15	
11	96/60	125¾	0	1,660	1.86	0.63	0.020			+1.13	
10	92/60	126	0	1,335	1.74	0.60	0.013			+0.88	
9	100/68	126	0	1,410	1.74	0.85	0.013			+0.21	
8	100/64	125½	0	1,770	*1.45	1.23	0.013		0.06	+1.33	
7	92/60	124	0	1,270	2.39	0.99	0.013		0.01	+1.11	
6	92/56	125	0	1,230	2.39	1.26	0.013			+1.21	
5	105/70	125	0	1,250	2.39	1.07	0.107			+1.96	
4	95/72	125	0	1,070	2.34	0.27	0.107			+0.05	
3	94/78	125½	0	1,660	2.34	2.18	0.107		0.07	+1.53	
2	106/78	125¾	0	1,420	2.34	0.63	0.107			+1.24	
1	110/86	125½	0	1,325	1.88	0.53	0.107				

In a previous paper by us,⁴⁸ the retention of sodium and water in pregnancy was attributed to the high estrogen and progesterone content of the body fluids. The evidence for this theory was found partly in reports from the literature indicating the sodium and water retaining properties of the estrogens and progesterone, partly from our own correlation of urinary estrogen and pregnanediol with sodium balance before and after labor.

a. The water and sodium retaining effects of the estrogens, and to some extent of progesterone, are evident from several types of observation. A retention of salt and water during the phase of sexual skin swelling of monkeys has been noted repeatedly;^{20, 32} retention of sodium and water also precedes menstruation in women.⁵² The injection of estrogens results in the retention of sodium and water in dogs⁵¹ and in monkeys.²⁵ Progesterone in large doses, 15 to 20 mg., has a similar effect in dogs.⁵¹

That a large proportion of the unexcreted water may be found in the organs of reproduction is true,^{2, 3, 47} but other organs partake in a general redistribution.⁵⁶ Clarke^{9, 10} noted an increase in extracellular fluid and in a few observations slight hemoconcentration at the time of sexual skin swelling in the baboon. This is in some contrast to observations made several years ago of pronounced increase in blood volume in women and animals after the injection of relatively small quantities of estrogenic substance.²²⁻²⁴ Selye and Bassett's⁴³ observation of a diuretic action of progesterone is also difficult to reconcile with other observations. Perhaps particularly relevant is a recent communication of Cantarow and Rakoff⁶ who found that progesterone, as well as desoxy corticosterone, increased the rate of diffusion of sodium and chloride into the peritoneum. These observations, in the opinion of the writers, supported the view that such agents have an effect upon membranes in general and that the decreased excretion of sodium and chloride produced by them might be simply secondary to extrarenal phenomena.

b. In our previous publication,⁴⁸ complete sodium balances were determined on 6 pregnant women for at least ten days before and ten days after delivery. It was noted that in all estrogen and pregnanediol excretion ceased shortly before the previously positive sodium balance became negative and the post-partum diuresis commenced. In one case intrauterine fetal death before the onset of labor was preceded by a sharp decrease in estrogens and pregnanediol in the urine and by a negative sodium balance beginning nearly four weeks ante partum. In a final case it appeared that the administration of estrogens in the puerperium reduced the loss of sodium. It was concluded that certain of the placental hormones, notably the estrogens, were factors in the retention of sodium during pregnancy.

The present communication reports the results of the administration of estrogens and progesterone on the excretion of sodium during pregnancy and in the puerperium. This work was undertaken for two purposes.

a. *Hormones During the Puerperium.*—The increased excretion of sodium and water during the puerperium is quite evidently a reflection

TABLE II. EFFECT OF ESTRADIOL BENZOATE ON SODIUM BALANCE IN TOXEMIA OF PREGNANCY (CASE 7)

DAYS	BLOOD PRESSURE	CLINICAL			SODIUM BALANCE						TREATMENT
		WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	
23		154	4.0	1,580	2.06	2.32	0.030		0.066	-0.36	
22		153½	3.6	1,270	2.06	1.78	0.030			+0.25	
21		153½	3.8	1,610	2.06	2.15	0.030			-0.12	
20		152	3.2	1,180	2.06	1.58	0.030			+0.45	
19		153	4.0	1,450	2.06	2.54	0.030			-0.51	
18		151½	4.0	1,085	2.06	1.51	0.030			+0.32	
17		152¼	3.0	1,420	2.02	2.00	0.015			0.00	
16	162/118	153	3.4	1,040	2.02	1.68	0.015		0.066	+0.26	
15	160/115	152	3.8	1,940	2.02	2.33	0.015			-0.33	
14	160/120	152¼	4.2	2,105	2.02	2.47	0.015			-0.47	60,000 R. U.
13	152/115										
	164/108	152	4.8	1,880	2.02	2.24	0.015			-0.24	60,000 R. U.
12	150/104	152	4.4	1,210	2.02	1.45	0.015			+0.48	60,000 R. U.
11	148/100	153	3.0	1,740	*1.74	1.67	0.129		0.075	-0.06	
10	146/108	153	3.6	2,095	2.02	2.45	0.129			-0.56	
9	148/104	152	3.6	1,865	2.02	1.77	0.129		0.058	+0.06	
8	136/104	152	3.2	1,170	*1.08	0.88	0.129			+0.07	
7	168/124	150	4.2	890	2.02	0.63	0.040			+1.35	
6	176/126	151	5.2	890	2.02	0.53	0.040			+1.45	
5	168/128										
	150/112	152	5.0	950	2.02	1.03	0.40			+0.95	
4	152/108	152¼	4.2	1,750	2.02	1.10	0.040			+0.88	
3	160/124	153	5.4	1,050	2.35	0.93	0.078		0.103	+1.34	
2	150/110	154	5.0	1,230	2.35	0.68	0.078			+1.49	
1	144/110										
	138/102	155	4.4	1,280	2.35	0.63	0.078			+1.64	

Day of labor	110/86 85/50 92/58	125	0 Trace Trace 0 0 0 0 0 0 Trace 0 0	964 1,575 1,545 1,350 1,680 1,870 1,480 1,435 1,880 1,850 1,705 1,295 1,530 1,730 1,400	*1.95 2.38 2.76 2.76 2.76 2.12 2.12 2.12 2.22 2.22 2.08 2.44 2.44 2.44 2.44	2.68 0.41 0.87 1.36 4.60 0.96 1.08 1.95 2.30 2.13 0.57 0.37 0.21 2.34 1.09	0.367 0.028 0.028 0.028 0.028 0.028 0.026 0.026 0.026 0.026 0.026 0.026 0.026 0.026 0.026	1.364 0.254 0.254 0.127 0.127 0.127 0.206 0.206 0.206 0.140 0.140 0.140 0.045 0.045 0.045	0.14 0.06 0.06 0.05 0.07 0.06 0.01 0.01 0.08 0.01 0.06 0.01 0.01 0.07 0.01	-2.00 +1.63 +1.55 +1.20 -2.07 +0.95 +0.80 -0.07 -0.39 -0.09 +1.28 +1.92 +2.18 -0.02 +1.30	60,000 R. U. 60,000 R. U. 60,000 R. U. 60,000 R. U. 60,000 R. U. 60,000 R. U.
1			Trace	1,575	2.38	0.41	0.028	0.254	0.06	+1.63	60,000 R. U.
2			Trace	1,545	2.76	0.87	0.028	0.254	0.06	+1.55	60,000 R. U.
3			0	1,350	2.76	1.36	0.028	0.127	0.05	+1.20	60,000 R. U.
4			0	1,680	2.76	4.60	0.028	0.127	0.07	-2.07	60,000 R. U.
5			0	1,870	2.12	0.96	0.028	0.127	0.06	+0.95	60,000 R. U.
6			0	1,480	2.12	1.08	0.026	0.206	0.01	+0.80	60,000 R. U.
7			0	1,435	2.12	1.95	0.026	0.206	0.01	-0.07	60,000 R. U.
8		114	0	1,880	2.22	2.30	0.026	0.206	0.08	-0.39	60,000 R. U.
9		113	0	1,850	2.22	2.13	0.026	0.140	0.01	-0.09	60,000 R. U.
10		113	0	1,705	2.08	0.57	0.026	0.140	0.06	+1.28	60,000 R. U.
11		112	0	1,295	2.44	0.37	0.026	0.140	0.01	+1.92	60,000 R. U.
12		113	Trace	1,530	2.44	0.21	0.026	0.045	0.01	+2.18	60,000 R. U.
13		114	0	1,730	2.44	2.34	0.026	0.045	0.07	-0.02	60,000 R. U.
14		114	0	1,400	2.44	1.09	0.026	0.045	0.01	+1.30	60,000 R. U.

*On this day part of food was refused or vomited. The figure for sodium intake was obtained by analyzing vomitus or rejected food and subtracting this from the sodium of the twenty-four-hour diet.

TABLE III. EFFECT OF ESTRADIOL ON SODIUM BALANCE IN A NORMAL PREGNANCY AND PUERPERIUM (CASE 8)

DAYS	BLOOD PRESSURE	CLINICAL			SODIUM BALANCE						TREATMENT
		WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	
10		134	0	1,725	2.53	1.14	0.005		0.113	+1.27	
9		134	0	2,120	2.53	1.95	0.005			+0.58	
8		134	0	1,615	2.53	1.68	0.005			+0.85	
7		135	0	1,875	2.53	2.10	0.005			+0.43	
6		135	0	2,185	2.53	3.51	0.005			-0.99	
5		134	0	1,615	2.51	1.63	0.012			+0.87	
4		134½	0	1,900	2.51	1.62	0.012			+0.88	
3		135	0	2,425	2.51	1.81	0.012		0.113	+0.58	10 mg. estradiol
2		135	0	2,325	2.51	2.64	0.012			-0.14	10 mg. estradiol
1		135	0	2,100	2.51	1.91	0.037		0.091	+0.47	
Day of labor											
1			0	2,640	*2.39	1.60	0.037	0.213	0.837	-0.30	5 mg. estradiol
2			0	2,155	2.51	1.28	0.009	0.279	0.100	+0.84	5 mg. estradiol
3			Trace	2,115	2.04	2.12	0.009	0.249		-0.34	5 mg. estradiol
4			Trace	2,465	2.04	2.18	0.009	0.127	0.102	-0.28	5 mg. estradiol
5			Trace	2,170	2.04	2.72	0.009	0.127		-0.92	5 mg. estradiol
6			Trace	1,760	2.04	2.59	0.009	0.090		-0.65	
7			Trace	1,815	2.04	1.71	0.009	0.060		+0.26	
8			Trace	2,195	2.04	1.81	0.005	0.060		+0.17	
9			Trace	2,295	2.04	2.46	0.005	0.040		-0.47	
10			0	1,970	2.09	1.30	0.011	0.040		+0.74	
11			0	2,600	2.09	2.94	0.011	0.040		-0.90	
12		124	Trace	1,960	2.09	2.23	0.011	0.040		-0.19	
13	130/80	124½	Trace	1,500	2.09	1.12	0.011	0.008		+0.95	
			Trace	2,775	2.09	2.32	0.011	0.008		-0.25	

*See footnote, Table I.

[illegible]

*See footnote, Table I.

TABLE V. EFFECT OF PROGESTERONE ON SODIUM BALANCE IN TOXEMIA OF PREGNANCY (CASE 10)

DAYS	CLINICAL				SODIUM BALANCE						TREATMENT
	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	
53	110/76	163½	1.5	1,300	2.23	1.51	0.018			+0.70	
	124/100										
52	125/86	163½	1.5	1,240	2.23	1.27	0.018			+0.94	
	124/102										
51	121/85		2.0	915	2.23	1.38	0.018			+0.83	
	124/100										
50	108/80	165	1.5	1,390	2.23	1.04	0.098			+1.09	
	118/92										
49	108/84	165	1.4	638	2.23	1.27	0.098			+0.86	
	130/98										
48	125/95	165	1.5	875	2.23	1.40	0.098			+0.73	
	130/105										
47	115/80	165	1.0	690	2.47	1.45	0.098			+0.92	
	110/86										
46	110/84		1.2	840	2.47	1.47	0.032		0.065	+0.90	25 mg. progesterone
45	120/94	163½	1.4	798	2.47	1.78	0.032			+0.66	25 mg. progesterone
44	120/80	163½	1.2	830	2.47	1.34	0.032			+1.10	
43	116/88	163½	1.2	740	2.47	1.27	0.032			+1.17	
	120/100										
42	116/184	163½	1.5	1,050	2.47	1.48	0.032		0.080	+0.88	
	110/80										
41	126/86	165	1.4	1,340	2.25	1.94	0.023			+0.29	
	128/86										
40	120/80	164½	1.4	1,090	2.25	1.86	0.023			+0.37	
	126/96										
39	118/88	165	1.5	675	2.25	1.82	0.023			+0.41	
38	128/84	165½	1.4	600	2.25	1.87	0.023			+0.36	
37	135/90	166	1.6	670	2.25	1.97	0.027			+0.25	

TABLE IV. EFFECT OF PROGESTERONE ON SODIUM BALANCE IN A NORMAL PREGNANCY AND PUERPERIUM (CASE 9)

DAYS	BLOOD PRESSURE	CLINICAL			SODIUM BALANCE						TREATMENT
		WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	
11	110/80	128½	0	2,110	2.59	1.71	0.018		0.071	+0.79	
10	100/80	129	0	2,000	2.59	1.74	0.018			+0.83	
9	114/76	129	0	1,960	2.59	1.82	0.018			+0.75	
8		130	0	2,390	2.31	2.11	0.018			+0.18	
7		130	0	2,250	2.85	1.64	0.007			+1.23	
6	112/80	130	0	2,340	2.85	1.94	0.007			+0.90	
5		129½	0	2,460	2.85	2.35	0.007		0.078	+0.42	
4	115/91	129½	0	2,200	2.85	2.26	0.007			+0.58	
3	109/91	129½	0	2,410	2.85	1.85	0.014		0.090	+0.99	
2	114/94	129½	0	2,185	2.85	2.68	0.014			+0.07	
1		129½	0	2,500	2.47	2.81	0.014			-0.35	
Day of labor	110/90		0	1,520	2.47	1.73	0.014	0.780	0.070	-0.12	25 mg. progesterone
1	120/85		0	2,300	2.47	4.55	0.070	0.086		-2.24	25 mg. progesterone
2			Trace	2,405	2.47	2.54	0.070	0.086		-0.30	25 mg. progesterone
3			Trace	2,960	2.47	3.54	0.070	0.240		-1.38	25 mg. progesterone
4			Trace	2,660	2.47	1.99	0.070	0.052		+0.36	25 mg. progesterone
5			Trace	3,030	2.58	2.89	0.070	0.052		+0.43	
6			Trace	2,675	2.58	2.77	0.070	0.051		-0.31	
7			Trace	2,385	2.58	1.68	0.070	0.051		+0.78	
8			Trace	2,165	2.58	2.09	0.070	0.048		+0.37	
9			Trace	1,790	2.58	1.80	0.067	0.048		+0.67	
10			Trace	2,335	2.58	2.20	0.067	0.050		+0.26	
11		119½	Trace	2,203	2.45	1.03	0.067	0.050		+1.30	
12		119½	Trace	2,350	2.45	1.26	0.067	0.024		+1.10	
13		119½	Trace	2,000	2.45	1.50	0.031	0.024		+0.90	
14		120	Trace	2,270	2.45	1.80	0.031	0.024		+0.60	
15		119½	Trace	2,420	2.45	2.49	0.031	0.024		-0.10	
16		120	Trace	2,190	2.45	1.98	0.031	0.022		+0.42	
17		120	Trace	2,125	2.45	2.06	0.040	0.022		+0.33	
18		120	Trace	2,265	2.45	2.19	0.040	0.022		+0.20	
19		120	Trace	2,510	2.45	1.63	0.057	0.022		+0.74	
20	115/90	120	Trace	2,490	2.45	1.37	0.057	0.022		+1.00	

TABLE V.—Cont'd

CLINICAL				SODIUM BALANCE						TREATMENT
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE
Day of labor	140/120		4.2	470	*1.40	0.87	0.167	1.182		-0.82
1	160/132									
2	130/90		1.8	1,250	2.17	3.60	0.021	0.377		-1.83
3	126/96		0.5	2,790	2.17	4.73	0.021	0.181		-2.76
4	126/100		2.0	1,345	2.17	3.06	0.021	0.253		-1.16
5	118/96		4.0	1,025	1.93	1.63	0.021	0.052		+0.16
6	120/100		4.0	840	1.93	0.99	0.021	0.052	0.065	+0.87
7	96/80		3.0	865	1.93	0.88	0.021	0.050		+0.98
8	116/96		2.8	815	1.93	0.85	0.021	0.050		+1.01
9	116/94		2.2	1,245	1.93	2.14	0.021	0.048		-0.28
10	112/94		2.6	1,740	1.93	2.27	0.021	0.048		-0.41
11		154	2.0	1,065	1.93	1.39	0.021	0.048		+0.47
12		154½	1.8	730	2.19	1.23	0.131	0.023		+0.81
13		154	2.0	1,400	2.19	1.57	0.131	0.023		+0.47
14		154	1.8	1,015	2.19	1.57	0.131	0.042		+0.45
15		155½	2.0	710	2.19	1.06	0.131	0.042		+0.96
16		153½	0.5	1,085	2.19	2.10	0.131	0.042		-0.08
	115/88	153	0.2	690	2.19	1.15	0.131	0.042		+0.87

*See footnote, Table I.

36	106/86	165½	1.6	690	2.25	2.00	0.027			0.067	100 mg. progesterone	+0.22
35	128/92	165	1.8	545	2.08	1.37	0.027				100 mg. progesterone	+0.68
34	134/92	166	1.5	1,140	2.08	2.71	0.041					-0.67
33	106/90	166½	2.0	1,120	2.08	1.80	0.041					+0.24
32	118/90	168	2.0	975	2.08	1.92	0.041					+0.12
31	116/88		2.5	840	2.08	1.76	0.041					+0.13
30	118/98		2.5	895	2.08	1.84	0.041					+0.50
29	125/104		2.0	1,495	2.16	1.62	0.041					+0.24
28	128/94	167½	1.6	1,410	2.16	1.83	0.093					-0.14
27	122/92	167	1.9	1,198	2.16	2.21	0.093					+0.07
26	136/98	167	2.4	570	2.16	2.00	0.093					+0.45
25	138/108	167	2.4	590	*2.03	1.49	0.093					+0.19
24	128/104	167	2.4	680	2.16	1.76	0.093					+0.99
23	95/75	166½	2.6	690	2.16	1.12	0.049			0.116	100 mg. progesterone	-0.35
22	128/102	166½	2.4	870	1.63	1.93	0.049					+0.18
21	134/100	167½	2.4	540	1.63	1.40	0.049					-0.45
20	128/84		2.2	780	1.63	2.03	0.049					+0.58
19	116/96	166		330	1.63	0.95	0.101					-0.72
18	128/108	165	2.2	670	*1.43	2.05	0.101					-0.58
17			2.4	710	1.63	2.11	0.101					+1.64
16	120/92	166	3.6	330	2.62	0.88	0.101					+0.33
15	114/90	166	3.4	730	2.62	2.19	0.101					+0.74
14	125/102	166	2.6	1,370	2.62	1.78	0.101					+1.31
13	120/94	166	2.6	980	2.62	1.21	0.101					+1.01
12	120/92	167	2.8	1,003	2.62	1.51	0.101					+0.92
11	124/94	168	3.8	690	2.62	1.60	0.101			0.116		-0.10
10	130/98	168	3.6	850	2.17	2.05	0.101					-0.11
9	110/84	169	2.8	810	2.17	2.18	0.101					-0.44
8	118/98	168	2.8	1,060	2.17	2.50	0.109					+0.28
7	120/96	168	2.6	1,200	2.17	1.78	0.109					-0.44
6	115/96	166½	3.6	820	2.17	2.50	0.109					-0.13
5	100/90	166½	3.1	1,015	2.38	2.40	0.109					+0.41
4	100/90	167	3.2	950	2.38	1.86	0.109					+0.35
3		167	4.4	885	2.38	1.92	0.109					+0.91
2	134/110	168	4.5	1,530	2.38	1.32	0.146					-0.14
1	124/106	168	4.8	1,003	2.38	2.32	0.146			0.058		

eral trends observed in the cases previously reported. These consist in a constant retention of sodium until the time of delivery with a negative balance appearing after parturition and reaching its greatest magnitude from the third to the fifth day. The days of greatest sodium loss correspond in general with the return of the urinary estrogen to nonpregnant levels. Summaries of the results of the balance studies are given in Table VI and in three graphs.

TABLE VI. SUMMARY OF SODIUM BALANCE OF FIRST TEN POST-PARTUM DAYS IN RELATION TO HORMONE ADMINISTRATION

NO.	PA-TIENT'S INITIALS	AGE	GRA-VIDITY	WEEK OF DELIVERY	DIAGNOSIS	HORMONE THERAPY	GAIN OR LOSS OF SODIUM IN GRAMS FROM THE DAY BEFORE DELIVERY TO THE TENTH POSTPARTUM DAY
1	M. M.	17	ii	Term	Normal	0	- 4.00
2	M. C.	36	ii	Term	Normal	0	- 6.59
3	M. P.	17	i	Term	Normal	0	- 4.08
4	L. D.	20	i	Term	Toxemia	0	-17.34
5	M. A.	25	i	36	Dead fetus.	0	- 2.56
					Toxemia		[-19.44]
6	M. M.	22	ii	Term	Normal	Estradiol benzoate	+ 2.78
7	F. P.	22	iv	Term	Toxemia	Estradiol benzoate	- 7.34
8	R. Y.	20	i	Term	Normal	Estradiol	- 1.85
9	H. L.	21	i	Term	Normal	Progesterone	- 2.34
10	A. Z.	20	i	Term	Toxemia	Progesterone	- 3.77

1. Effect of Administration of Hormones in the Early Puerperium.—Attempts to maintain in the puerperium levels of estrogen or progesterone characteristic of pregnancy failed, if one may judge from the assay of the urine specimens collected during those days. Under normal conditions the concentration of estrogen in the urine falls rapidly and immediately after delivery and a level characteristic of the non-pregnant woman is reached on the third, fourth, or fifth day. Daily injection of 30,000 rat units of estradiol benzoate or 5 mg. of estradiol failed to alter this post-partum decline in urine estrogen values to any extent. No change in the rate of decline of urinary pregnanediol was brought about by the use of 50 mg. of progesterone daily. Nevertheless, for two reasons it appears that the amounts given were physiologically effective. With due regard to body weight relationships, the dosage of both estradiol and progesterone was comparable with that by which Thorn and Engel⁵¹ obtained measurable effects on sodium excretion in dogs. It was further noteworthy that in none of the women treated by hormones in the puerperium was there any appreciable lactation.

Hormone Administration After Normal Pregnancy: In Chart 1 is shown the sodium balance for ten days before and ten days after delivery in six normal pregnancies, the eleventh ante-partum day being taken as the base line in each case. The first graph of the chart is a composite of balance studies previously reported on three normal untreated patients which serve as controls. The average loss of sodium

of some physiologic change caused by the loss of the fetus or the placenta. Although the final elimination of the estrogens and progesterone, with their known sodium retaining properties, seems a satisfactory explanation, other possible ones exist. As an example might be mentioned, the disappearance of the placental circulation which on account of its large arteriovenous communication has been held a competent cause of the increased blood volume and increased venous pressure in the lower extremities,⁴ and hence perhaps a factor in fluid retention. It was hoped that by administering large quantities of the estrogens or progesterone in the puerperium, concentrations of these substances characteristic of pregnancy might be maintained. Should, under these circumstances, the post-partum diuresis and sodium loss be prevented or delayed, the association of the original salt and water retention with the hormones of the placenta would be more or less established.

b. Hormones During Pregnancy.—The use of estrogens and progesterone has been suggested for the treatment of toxemia of pregnancy.^{45, 55} Yet the patient with toxemia is already suffering from an abnormal retention of sodium and water. Should further salt retention follow hormone administration, such therapy might actually be dangerous.

Methods

The women studied were all patients hospitalized on the New York University obstetrical service in Bellevue Hospital. Diets were prepared, as previously described by a special dietitian in a small kitchen adjacent to the ward. The daily intake of sodium was fixed at 2.37 Gm. a low figure being used because this was thought advisable in patients with toxemia of pregnancy. Although the food was weighed to give approximately the sodium content desired, actual measurements were carried out by analysis of a duplicate twenty-four-hour sample diet on every fourth day, at which time slight changes in composition but not in sodium content were made.

All urine, feces, lochia, amniotic fluid, and blood lost at delivery were collected and sent to the laboratory. Details of the manner of collection and of the analytical procedures have been previously described.⁴⁸ Estrogens, pregnanediol and prolactin (chorionic gonadotropin) were also measured on the urine specimens. The effect of the administration of the estrogens and progesterone on the hormone pattern of the urine will not, however, be reported here.

Clinical Material

The data obtained from five previously reported patients (Cases 1 to 5), whose sodium balances were studied during late pregnancy and the early puerperium without hormone administration were used as controls.⁴⁸ In contrast there are to be reported 5 patients who received hormones, either estrogen or progesterone, immediately after delivery in an effort to prevent or modify the sodium loss and diuresis of the early puerperium. In 3 of these patients large doses of hormones were also given during pregnancy to determine whether the sodium balance was in any way disturbed by such treatment.

Results

The sodium balance of the 5 hormone treated patients (Tables I, II, III, IV, and V) showed, with certain exceptions to be noted, the gen-

rat units of estradiol benzoate was administered during the first five post-partum days, there was an actual retention of 2.78 Gm. of sodium before the tenth day. In Case 7 in whom 45 mg. of estradiol were given during the week beginning with the second day before delivery, there was a total loss of only 1.85 Gm. of sodium in the first ten post-partum days. Progesterone showed less evidence of being effectual, but

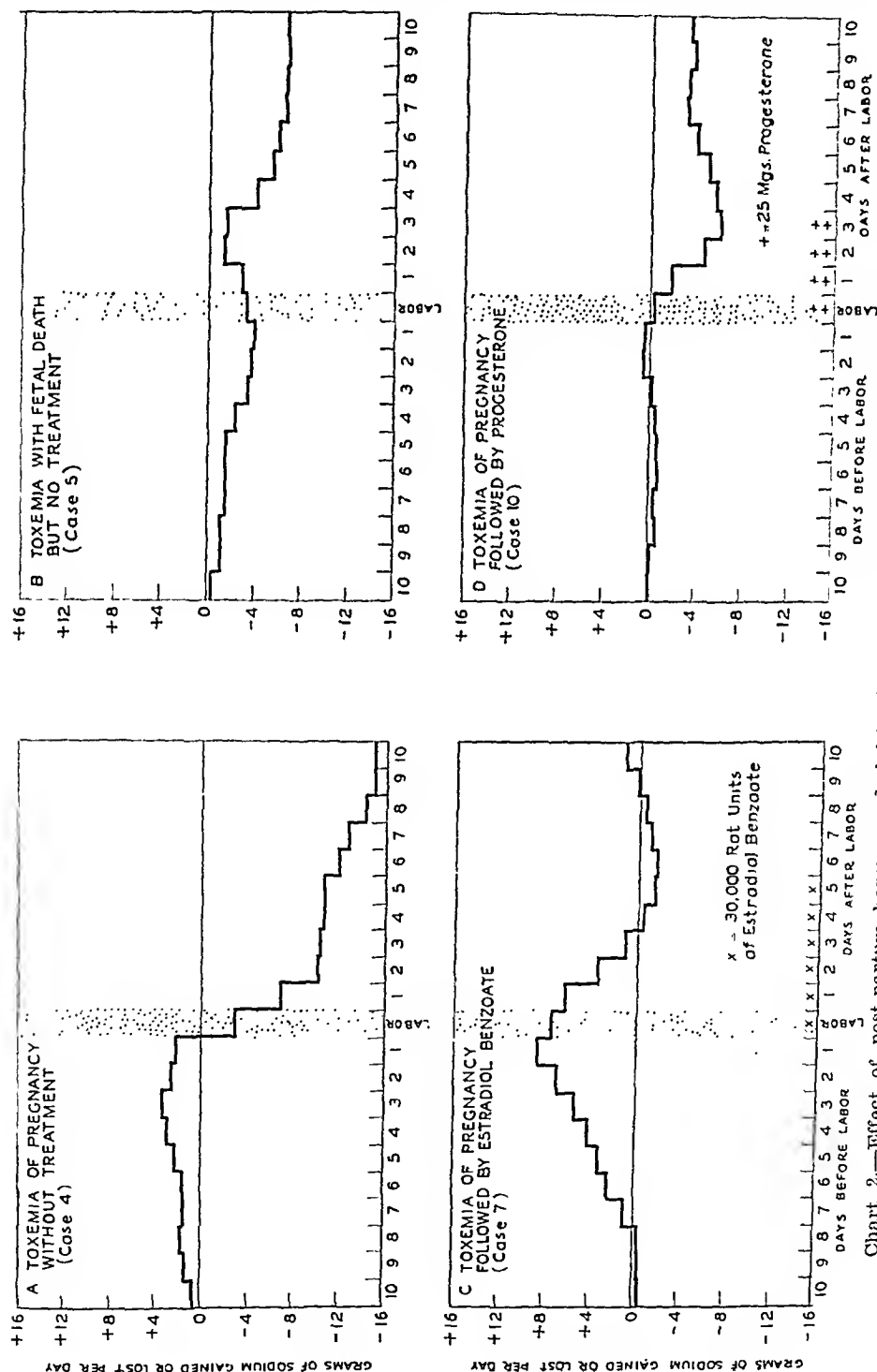


Chart 2.—Effect of post-partum hormone administration on sodium balance after toxemia of pregnancy.

in the first ten post-partum days in these three patients was 4.89 Gm., the individual loss in each case being 4.00, 6.59, and 4.08 Gm., respectively (Table VI).

Each of the remaining three normal cases received estradiol benzoate, estradiol, or progesterone and in each sodium loss was less than in any of the three untreated patients. In Case 6 in whom a total of 300.000

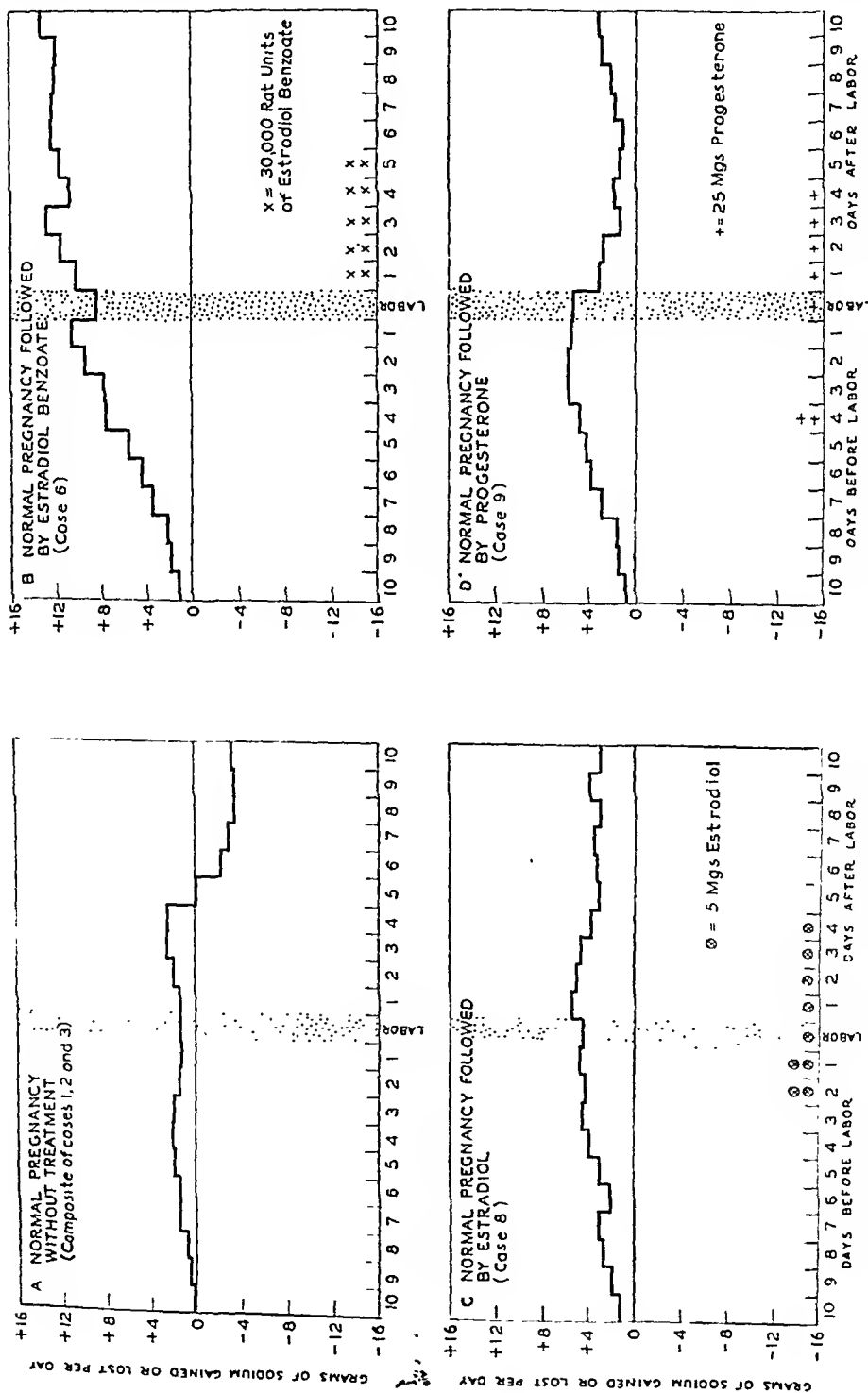


Chart 1.—Effect of post-partum hormone administration on sodium balance after normal pregnancy.

when 125 mg. were given the loss of sodium before the tenth day was only 2.34 Gm.

Hormone Administration After Toxemia of Pregnancy: The water and sodium lost after toxemia of pregnancy are subject to great variations, depending principally on the amount of previous edema. The problem of setting up controls for studies of sodium loss in these cases is therefore much greater than after normal pregnancy. In Chart 2 is shown the sodium balance before and after delivery in four cases with toxemia of pregnancy. In Case 4, the loss in ten days amounted to 17.34 Gm. of sodium. In Case 5, the ten-day loss amounted to only 2.56 Gm., but this patient had begun to lose sodium, probably as an accompaniment of impending intrauterine fetal death, three weeks before her delivery. If the sodium loss in this case were taken from the day in which a negative balance set in and were carried to the tenth post-partum day, the total loss would amount to 19.44 Gm.

In the two remaining patients, hormone administration was begun on the day of labor and in each the sodium loss was lower than in either of the other cases of toxemia. In Case 7, receiving 300,000 units of estradiol benzoate, 7.34 Gm. were lost, while in Case 10, receiving 200 mg. of progesterone, the loss was 3.77 Gm. of sodium. In each untreated case the balance was still negative on the tenth post-partum day, while in each treated case sodium was again being retained.

2. Effects of Administration of Hormones During Pregnancy.—In three cases hormones were administered before the end of pregnancy to determine whether sodium excretion could be influenced under these conditions. The results can be found in detail in the tables and are shown graphically in Chart 3.

Attempts to influence the course of pregnancy by the administration of any of the sex hormones have, to the present time, met with only doubtful success. The reason for this is probably to be found in the fact that the amount of hormone administered has usually represented a very small fraction of the amount being constantly manufactured by the patient herself. The fairly large doses of estrogen and progesterone given to the patients of this study during their pregnancy may also have represented an insignificant increase over their normal supply.

A normal patient (Case 6) received 180,000 rat units of estradiol benzoate distributed over a three-day period, beginning sixteen days before the onset of labor. A patient with toxemia (Case 7) received the same dosage, beginning fourteen days before her delivery. In each instance there were several days of slightly decreased sodium retention followed by a slightly increased positive balance. Case 10, a patient with toxemia, received progesterone on three separate occasions, in doses of 50 to 200 mg. given over forty-eight-hour periods. On none of these occasions was the sodium balance in any way affected. The urine volume likewise did not change in any consistent manner following these injections.

Discussion

The absence of the post-partum sodium loss in one and its apparent reduction in another case of normal pregnancy after estrogen treatment in the puerperium is additional evidence that one of the causes of sodium and water retention in normal pregnancy is the high estrogen concentration characteristic of the body fluids during that period. That

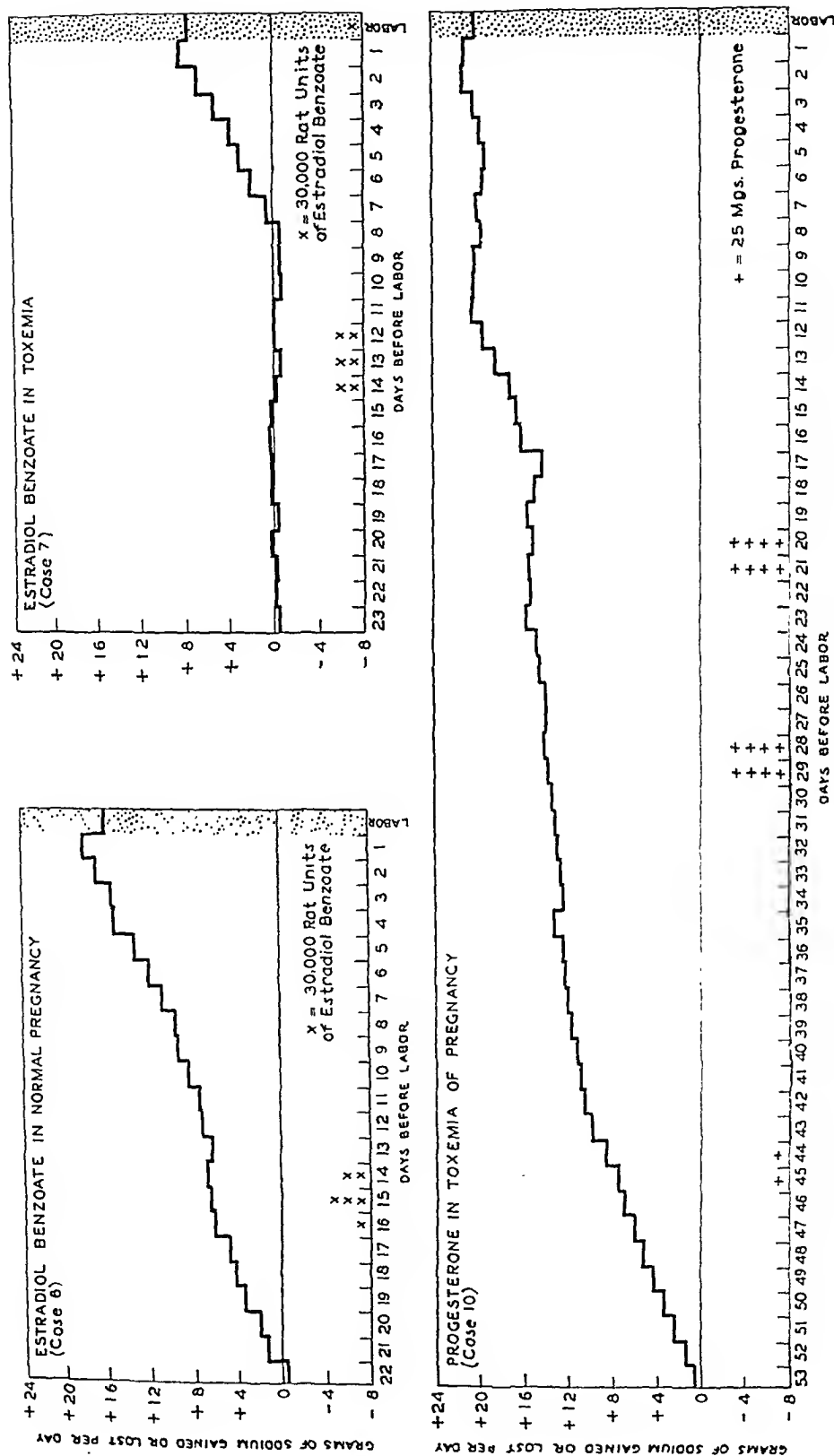


Chart 3.—Effect of ante-partum hormone administration on sodium balance during pregnancy.

strong evidence against an increased capillary permeability in normal pregnancy exists in the absence of proteinuria, for were there any general tendency to capillary injury this should affect the glomerular capillaries and protein should appear in the urine. In the toxemic patient, however, the characteristic development of proteinuria indicates an increased glomerular permeability to the plasma proteins. Such a change may well affect the capillaries more or less universally and might be the explanation of the great increase in fluid retention which takes place when the normally pregnant woman becomes toxemic as well.

e. An increase in venous pressure, which is present in the veins of the legs during pregnancy,⁴ undoubtedly favors the appearance of edema in the feet and ankles. This increased venous pressure in the legs may be due in part to the pressure of the large uterus on the vessels of the pelvis, in part to the structure of the placental circulation, in which a capillary bed is largely absent and conditions are thought to approximate those found in arteriovenous fistula.⁵ The increased blood volume has also been ascribed by Burwell⁵ to certain peculiarities of the placental circulation. The water of the lower extremities and that accounted for by the increased blood volume may represent a significant part of the total retained in normal pregnancy.

f. The general tendency of normal pregnant women to retain sodium and water appears, however, to be best explained by the fact that they are constantly under the influence of enormous quantities of the steroid sex hormones. This effect is so predictable from the known physiologic properties of these substances that were the tendency to sodium and water retention not present, one would have to find an explanation for its absence.

The increase in the tendency to sodium and water retention which takes place with the onset of toxemia does not, however, find a complete explanation on the basis of a further rise in hormone effectiveness. The sudden appearance of proteinuria and of hypertension and the change from hydremia toward hemoconcentration indicates that a new mechanism is at work. Furthermore, in most cases of preeclampsia, rates of steroid sex hormone excretion are not increased, but probably decreased. Although the estrogens and progesterone probably continue to contribute to the sodium retention in toxemia, the greater edema of that disease cannot be considered simply an exaggeration of that found in normal pregnancy.

During pregnancy the administration of what would now be regarded from the clinical standpoint as large doses of estrogen and progesterone had no demonstrable effect on sodium balance. It is believed that in relation to the enormous quantities of hormone produced daily by the pregnant woman the administered quantities were actually small, perhaps physiologically insignificant.

Conclusions

1. Among several factors which cause normal pregnant women to develop edema, the most important is probably the physiologic influence of the estrogens and progesterone on the excretion of sodium and water.

2. In the edema of specific toxemia, additional factors are almost certainly at work. Yet it is important to take into account the fact

progesterone may contribute to this is suggested by the case treated by this substance in which the loss of sodium in the early puerperium was relatively slight. The effect of estrogens and progesterone in preventing diuresis and sodium loss in the puerperium of patients who had had toxemia of pregnancy was less convincing but still suggestive.

The many factors which have been offered to explain the edema of pregnancy require a re-evaluation in the light of these effects of the sex steroids on sodium and water.

a. The ingestion of large quantities of sodium in the form of sodium chloride may increase the symptoms of toxemia, as de Snoo and Strauss have pointed out. The increase of extracellular water when sodium is administered is not, however, a peculiarity of pregnancy, but will occur to some degree in quite normal persons. That which is characteristic of both normal and toxemic pregnancy is the delayed elimination of sodium, so that a given quantity will be the cause of a greater degree of edema than in the nonpregnant person. To agree that excessive sodium retention is the immediate cause of the edema allows one, however, simply to transfer the problem to the cause of this increased tendency to sodium retention. The reasons for believing that the estrogens and progesterone are the cause of this physiologic change have been given.

b. A decrease in colloid osmotic pressure due to a reduction in plasma proteins may slightly increase the tendency to edema in the latter part of normal pregnancy. In exceptional cases with pronounced nutritional deficiencies a very low concentration of plasma protein may even be the major cause of the edema, but such cases are neither examples of normal pregnancy nor of pre-eclampsia. Diekmann's¹⁶ studies appear to have more or less disposed of the low plasma proteins as a primary or important contributing factor in the ordinary case of toxemia of pregnancy.

c. Although Diekmann¹⁶ has cited various observations suggesting that in normal pregnant patients "the renal function is altered if not actually temporarily impaired," the evidence for this point of view seems to us quite inconclusive. Studies of the last few years^{7, 12, 54} based on the renal clearance of inulin and diodrast indicate no disturbance in kidney function in normal pregnancy. The normal glomerular filtration rate as determined by the inulin clearance in particular makes it extremely unlikely that a decreased renal function contributes in any way to the moderate edema characteristic of normal pregnancy. In some patients with toxemia of pregnancy, it is true, there is evidence of a moderate reduction in the glomerular filtration rate.^{12, 18, 53} This might contribute slightly to the tendency to retain water, but the observed degree of reduction in this function would be wholly inadequate to produce any significant edema in the nonpregnant patient. It is further noteworthy that in a few of our toxemic patients in whom edema was present, the filtration rate was found to be quite normal. Such observations strongly suggest that the edema of both normal and toxemic pregnancy has an extrarenal cause.

d. In normal pregnant women some evidence for an increased capillary permeability has been found in various indirect tests which are said to have shown an increase in protein in the subcutaneous fluids.^{33, 35} Agreement on this point is, however, not complete.²⁹ On the other hand

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ANTECUBITAL AND FEMORAL VENOUS PRESSURE IN NORMAL AND TOXEMIC PREGNANCY*

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INTEREST in venous pressure in pregnancy has been aroused by the recent reports of Burwell and his collaborators¹⁻³ dealing with a variety of vascular and cardiac phenomena in the pregnant woman. These workers confirmed the earlier findings of Runge,⁴ who had demonstrated a considerable elevation of venous pressure in the lower extremities in the latter part of pregnancy, and they suggested that the abnormal venous pressure, as well as other disturbances in vascular physiology, might be explained on the basis of the fact that the placental circulation simulates an arteriovenous shunt. If it can be shown that the level of venous pressure is such as to impair normal fluid exchange in the arteriolar and venous limbs of the capillaries, the appearance of edema in pregnancy should be readily explainable. More remotely, such an effect on fluid movement might be given consideration as a factor in the development of the toxemias of pregnancy.

However, the numbers of venous pressure determinations in pregnancy thus far reported are insufficient to permit drawing final conclusions. The purpose of the present study was to establish standard values for venous pressure in both upper and lower extremities throughout pregnancy and in the immediate puerperium. For comparison with these figures it seemed desirable to obtain a series of determinations on patients suffering from the various forms of the hypertensive toxemias of pregnancy, particularly in view of the fact that the literature contains contradictions as to the levels of antecubital venous pressure during pregnancy toxemia and the further fact that no observations have been made of venous pressure in the lower extremities during toxemic episodes. Finally, in an attempt to throw further light on the

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that when the pregnant woman develops toxemia she is already physiologically conditioned to retain water readily. In this indirect sense at least the estrogens and progesterone may contribute greatly to the clinical manifestations and course of the disease.

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18.1 cm. Landt and Benjamin¹⁴ made repeated venous pressure observations on 19 women who were followed throughout pregnancy and the puerperium. They concluded that arm venous pressure was moderately high in early pregnancy, decreased slightly until the end of the sixth or seventh month, and then rose gradually until delivery occurred. The range of values was 4.8 to 11.0 cm., and it was pointed out that all of the values fell in the "normal range." Cohen and Thomson¹⁵ made 41 observations of arm venous pressure in ten patients; five observed ante partum had a range of venous pressure from 4 to 12 cm. of water and five post-partum patients had pressures from 6.4 to 12 cm. Luisi¹⁶ found that 13 normally pregnant women had venous pressures ranging from 1.8 to 15.0 cm. of water, while 29 subjects with various types of pregnancy toxemia had a venous pressure range of 2.0 to 14.5 cm. of water. He concluded that venous pressure in the arm increases during normal pregnancy, that the increase is more marked during parturition and in the few hours after delivery, and that it returns to normal during the puerperium.

Perhaps the most important contribution to the subject of venous pressure in pregnancy has been that of Burwell and his co-workers.¹⁻³ Their preliminary studies indicated that in nonpregnant persons without heart disease or local venous obstruction, venous pressures measured with the subject lying in bed were of the same general magnitude in the arm and in the leg (femoral vein). In 24 observations of both antecubital and femoral venous pressures in 22 pregnant women from the third month of gestation to term, the arm values ranged from 5.1 to 15.6 cm. of water and the femoral vein pressures from 7.8 to 26.5 cm. of water. It appeared that there was an abnormal rise in femoral venous pressure by the beginning of the second trimester of pregnancy, and that this elevation persisted and even increased throughout pregnancy. After delivery the femoral venous pressures returned to normal levels. Burwell and others³ also observed pressures in jugular, femoral, and uterine veins of 12 pregnant bitches. With the animals supine and under barbitol anesthesia it was found that the pressures in the femoral veins were higher than those in the jugular veins. This difference in pressure was diminished or absent after the uterus was removed. Opening the abdominal cavities of the pregnant animals did not appreciably lower the femoral venous pressures. Lifting the gravid uterus from its normal position and supporting it in such a way that it no longer pressed on the large veins produced a fall in femoral pressure but the latter usually remained above the pressure in the jugular vein. After the uterus was surgically removed the femoral venous pressure approached that in the jugular vein in 5 of 6 animals in which comparative measurements were made. In six pregnant bitches pressure determinations were made in broad ligament veins which presumably drained uterine wall and placental site; these uniformly exhibited higher pressures than the femoral veins. In nonpregnant, anesthetized dogs distended by injecting physiologic solution of sodium chloride into their abdominal cavities it was noted that the abdominal wall was tense when femoral venous pressure reached a level comparable to that in pregnant animals. But, since the abdominal wall of the pregnant bitch or pregnant woman is not tense even in the presence of a markedly elevated femoral venous pressure, it was concluded that the elevated femoral venous pressure observed during pregnancy is not the result of an increase in intra-abdominal pressure.

nature of the mechanism responsible for the elevation of venous pressure below the level of the pregnant uterus, the portions of the study dealing with pelvic tumors, intrauterine fetal death, and venous pressure during delivery were carried out.

Review of Literature

Comparatively few studies of venous pressure during pregnancy have been made and most of them are concerned only with pressure in the veins of the upper extremity. While Runge⁴ commonly receives credit for making the first such observations, Fuchs⁵ published a few inconclusive determinations of venous pressure in pregnancy three years earlier. Runge observed venous pressure directly by the method of Moritz and von Tabora⁶ in 34 normal pregnant women, 7 post-partum patients, and 6 essentially normal gynecologic patients. The average pressure in the saphenous vein was slightly elevated prior to the seventh month of gestation and was decidedly elevated during the last trimester. In 16 patients observed during the tenth lunar month, the venous pressures in the legs ranged from 10.7 to 31.4 cm. of water, with an average value of 20.3 cm. of water. Runge suggested that the increased pressure in the lower extremities during pregnancy resulted from the increased quantities of blood returning through the pelvic veins to the main venous trunks rather than from simple mechanical compression of large veins by the growing uterus.

Kaboth⁷ found the arm venous pressure to be slightly elevated in the last half of pregnancy, and in two patients with eclampsia and edema the venous pressure ranged from 16 to 25 cm. of water. Villaret, Saint-Girons and Salas⁸ measured both arm and leg (saphenous vein) pressures with an aneroid manometer in five pregnant women "near term"; the ranges were 12 to 15 cm. in the arm and 31 to 42 cm. of water in the leg. Dellepiane⁹ found that the venous pressure in the arm during normal pregnancy ranged from 10 to 16 cm. of water, while immediately post partum it was 18 to 22 cm. of water.

Krukenberg¹⁰ reported that the average venous pressure in the arm in 29 normal pregnant women was 5.69 cm. of water. Baráth and Weiner¹¹ obtained venous pressure readings on 11 pregnant patients without edema and plotted them against colloid osmotic pressure values for the same individuals. From their graph it appears that the venous pressures in the arm ranged from 11 to 18 cm. of water, while 11 normal individuals had venous pressures ranging from 4 to 7 cm. of water. Strauss¹² determined directly the venous pressures in the arms of 20 normally pregnant women during the last two months of gestation. The values ranged from 3 to 18 cm. of water and the average was 10 cm. For comparison, 20 pregnant patients in the last trimester, with arterial blood pressures of 150/100 mm. Hg or higher, had venous pressures ranging from 8 to 20.5 cm. of water, averaging 13.3 cm. From these observations Strauss concluded that arm venous pressure often was above the upper limits of normal in uncomplicated pregnancy and was commonly elevated to abnormal levels in pregnancy toxemias.

Róna¹³ reported 53 values for cubital vein pressure during the last trimester of pregnancy. They ranged from 3.0 to 19.4 cm. of water and averaged 10.4 cm. The arterial blood pressures of some of these patients fell in the "toxemia" range. Twenty-two values for venous pressure in leg veins ranged from 3.7 to 29.3 cm. of water and averaged

during pregnancy. Only two investigators have attempted to demonstrate a gradient of pressure in the leg as pregnancy advanced, and the numbers of observations reported by them are too few to permit definite conclusions. There have been no observations on venous pressure in the lower extremity during pregnancy toxemia.

Apparatus, Material and Method

The apparatus used to determine venous pressure directly was essentially the same as that described originally by Moritz and von Tabora,⁶ namely, a water manometer, a reservoir for saline solution connected to the manometer and to an intravenous needle by means of suitable rubber tubing and a Y-tube (replaced by a 3-way glass stopcock). The glass manometer tube had a bore of 2 mm. and was mounted on a wooden standard which could be adjusted vertically by means of a sliding central panel. A meter stick with a spirit level attached centrally along one edge served as a leveling device. The intravenous needles were 19-gauge, those used in the arm veins being $1\frac{1}{2}$ inches long, those for the femoral veins $2\frac{1}{2}$ inches. The apparatus was filled with a 1 per cent solution of sterile sodium citrate in physiologic saline for all except the prolonged observations on patients undergoing operations; for the latter a 3 per cent citrate solution was used.

Seven hundred fifty-seven determinations of venous pressure were made in 255 different subjects. Three hundred forty-five determinations were made in the antecubital vein and 412 in the femoral vein. Thirty of the subjects were normal controls, consisting of nurses and ambulatory patients from the gynecological service of the University of Minnesota Hospitals. One hundred fifty-eight subjects were normally pregnant women from the obstetrical services of the University of Minnesota Hospitals, the University of Virginia Hospital, and the Booth Memorial Hospital of St. Paul, observed during pregnancy and/or the puerperium in a total of 160 pregnancies. From the same sources there were 55 women with some form of hypertensive toxemia of pregnancy observed in 57 different pregnancies. Twelve patients with a variety of abdominopelvic tumors were from the gynecologic service of the University of Minnesota Hospitals.

All determinations were made on recumbent (supine) subjects who had rested in that position for at least ten minutes. In the arm the technique was essentially that advised by Lyons, Kennedy and Burwell.²² Readings were made to the nearest 0.5 cm. except in the case of the control subjects, where readings were made to the nearest millimeter. If the column of fluid in the manometer fell unusually slowly or if the level at which it settled out was above the supposed upper limit of normal (i.e., 12 cm. of water), possible sources of error in the technique or in the positioning of the extremity were searched for and corrected.

In the lower extremity, the technique was similar to that described by Ferris and Wilkins.²³ Occasionally the femoral artery was entered accidentally; when this occurred the needle was removed from the thigh and the blood which had rapidly extended well above the level of the adapter was washed out. The needle then was reinserted somewhat more medially than at the first trial. At the conclusion of each determination, digital pressure was maintained at the venipuncture site for one or two minutes to prevent the formation of a hematoma. In the

During a study of blood volume in pregnancy, Thomson, Hirsheimer, Gibson and Evans¹⁷ determined directly arm venous pressures in 15 normal pregnant women at various stages of gestation. Their range of values was 2.5 to 11.3 cm. of water. Thomson, Reid and Cohen¹⁸ have reported a series of arm venous pressure determinations in normal pregnant women, pregnant women with compensated and decompensated heart disease, and in women with toxemias of pregnancy. In twenty normal pregnant women 65 ante-partum values and 29 post-partum values fell in the normal range. They stated that the average venous pressure values were slightly higher in early pregnancy than in mid and late pregnancy and the puerperium. It was noted that 9 of 15 observations made during the first two weeks of the puerperium were higher than the corresponding final ante-partum values. Venous pressure in 27 compensated cardiac patients throughout pregnancy and the puerperium fell within normal limits, while 18 patients who developed cardiac failure during pregnancy also exhibited arm pressures within the normal range, except in one instance where there was massive edema. However, where pre- and post-failure observations were made, the venous pressure was higher when there were signs of heart failure. In 21 women with toxemia of pregnancy the venous pressure values did not exceed 14 cm. of water, which these workers considered the extreme upper limit of normal, but more of the toxemia values fell in the upper normal range than did values in the nontoxemic pregnant group.

Veal and Hussey¹⁹ have studied the venous circulation in the lower extremities during pregnancy by measuring venous pressure directly in the popliteal vein while the patient was standing. These workers have used an "exercise test" in an attempt to demonstrate that women with edema or varicosities have more severe venous obstruction than those without such phenomena. It is their belief that ordinary measurements of femoral venous pressure fail to demonstrate this difference, since the venous system may be adequate during rest and inadequate with activity.

Hamilton and Thomson's monograph²⁰ on the heart in pregnancy contains a reference to 7 observations of ante-partum femoral venous pressure which varied between 12.5 and 25.0 cm. of water. The other values mentioned in this work were taken from the paper of Thomson, Reid and Cohen.¹⁸ In their monograph on pre-eclamptic and eclamptic toxemia, Dexter and Weiss²¹ have noted that the arm venous pressure in 9 normal pregnant women without edema, albuminuria, or hypertension averaged 10.4 cm., and in 18 patients with edema and various types of toxemia, the average was 10.1 cm. of water. On the basis of these observations they concluded that variations in venous pressure were not related to degrees of edema, hypertension, or albuminuria, and that hydrostatic pressure in the capillaries played no essential part in the formation of the edema of pregnancy.

In summary, 8 reports list values for arm venous pressures in pregnancy which are in excess of 14 cm. of water, a value which is frequently spoken of in the general literature as being the extreme upper limit of normal. The values in the other eight reports dealing with arm pressures fall into the so-called normal range. Of the five reports which include determinations made in patients with toxemia of pregnancy, all indicate that the arm venous pressure values *may* lie above normal limits, although this specific conclusion was reached by only two of the authors. There are 7 reports on venous pressure in the lower extremity and all indicate that the values are elevated above normal

TABLE I. MEANS, STANDARD DEVIATIONS AND STANDARD ERRORS OF MEANS FOR ANTECUBITAL AND FEMORAL VENOUS PRESSURE AT VARIOUS STAGES OF NORMAL AND TOXEMIC PREGNANCY

WEEKS OF GESTATION OR DAYS POST PARTUM	ANTECUBITAL VENOUS PRESSURE, CM. WATER				FEMORAL VENOUS PRESSURE, CM. WATER			
	NUMBER OF VALUES IN SAMPLE	MEAN	STAND- ARD DEVI- ATION	STAND- ARD ERROR OF MEAN	NUMBER OF VALUES IN SAMPLE	MEAN	STAND- ARD DEVI- ATION	STAND- ARD ERROR OF MEAN
<i>A. Normal pregnancy</i>								
5-12	7	7.85	1.93	1.02	7	9.14	3.54	1.45
13-16	7	8.07	3.56	1.46	7	14.00	7.69	3.14
17-20	5	7.60	3.20	1.60	5	14.60	3.78	1.89
21-24	11	8.95	2.31	0.73	15	17.83	3.28	0.88
25-28	4	10.75	2.87	1.66	6	21.00	2.57	1.15
29-32	10	7.15	2.27	0.76	12	22.29	2.76	0.83
33-36	19	6.97	1.64	0.39	27	21.33	4.09	0.80
37-38	9	7.11	2.85	1.01	18	22.94	3.89	0.94
39-40+	42	7.64	2.52	0.39	50	24.37	4.61	0.65
5-40+ (all ap.)	114	7.72	2.45	0.23				
1-2	16	8.91	2.69	0.69	26	10.08	1.81	0.36
3-4	16	7.94	1.97	0.51	21	9.64	2.53	0.57
5-9	21	7.59	2.19	0.49	27	9.04	2.43	0.48
10-20	6	7.42	2.14	0.96	6	10.00	3.86	1.73
3-20	43	7.70	2.03	0.31	54	9.38	2.60	0.35
1-20 (all pp.)	59	8.03	2.26	0.29	80	9.61	2.37	0.27
<i>B. Toxemic pregnancy</i>								
5-12	2	9.75			2	13.50		
13-16	1	5.50			1	8.00		
17-20	2	6.75			2	11.00		
21-24	2	9.50			2	14.25		
25-28	3	9.33	2.27	1.61	3	21.33	3.57	2.53
29-32	9	8.11	3.63	1.28	8	18.88	3.06	1.16
33-36	9	9.44	3.44	1.22	11	20.86	5.07	1.60
37-38	20	6.88	2.18	0.50	21	23.07	3.22	0.72
39-40+	24	8.75	3.91	0.82	27	22.22	4.86	0.95
5-40+	72	8.21	3.29	0.39				
1-2	9	12.39	4.01	1.42	10	13.05	4.38	1.46
3-20	17	8.59	3.55	0.89	23	9.22	2.59	0.55

pregnancy (Tables I and II, H, Figs. 2 and 3). While the mean pressure prior to the thirteenth week of pregnancy fell just below the control mean minus three standard errors, the means for all the subsequent gestational periods were clearly above the average for the controls. However, the numbers of individual measurements from thirteen to twenty weeks were small and their variations relatively great, with the result that a statistically significant difference between pregnant and nonpregnant femoral vein pressures was not demonstrated prior to twenty-one weeks (Table II, H). In the thirty-ninth and fortieth (or more) weeks of pregnancy, the mean femoral venous pressure was 24.37 ± 0.65 cm. of water (17.9 ± 0.47 mm. Hg). It fell abruptly following delivery, so that the mean value during the first forty-eight hours post partum was 10.08 ± 0.36 cm. of water, i.e., essentially that of the nonpregnant controls. The two subsequent post-partum groups, three to four and five to nine days, showed average pressures which were significantly lower than the controls (see Table II, H) while the

prolonged observations on patients undergoing abdominal operations the needle was briefly flushed with solution from the reservoir at intervals of three to four minutes in order to prevent clotting of blood in the relatively small lumen. Manometer readings were recorded at intervals of one-half to five or ten minutes, depending upon the rapidity of the observed changes in venous pressure.

The statistical expressions were computed by the usual formulae, as given by Treloar.²⁴ When the probability of a difference between means being the result of an error of random sampling was open to question because of smallness of the sample (less than 30), the probability factor (P) was recalculated by Fisher's²⁵ small sample formula and table of "t" values.

Results

1. *Normal Controls.*—In 30 normal females, ranging in age from 13 to 48 years, the mean value for antecubital venous pressure in the supine posture was 7.88 cm. of water and for femoral venous pressure was 11.43 cm. of water. The respective standard deviations were 1.64 and 3.43 and the standard errors of the means were 0.31 and 0.64. The coefficient of variation was somewhat smaller for the arm pressure values, being 21 per cent, as compared with a coefficient of variation of 30 per cent for the femoral pressure measurements. The difference of 3.55 cm. of water between the mean values for antecubital and femoral venous pressure is statistically significant, since this difference is more than five times as great as its standard error (Table II, A).

2. *Normally Pregnant Subjects.*—In 158 normally pregnant or post-partum women observed in 160 pregnancies, 400 determinations of venous pressure were made, 261 of them ante partum and 139 post partum. The mean antecubital venous pressure in 114 ante-partum determinations was 7.72 ± 0.23 cm. of water and in 59 post-partum determinations was 8.03 ± 0.29 cm. of water. The difference between these two values is not statistically significant, as may be seen from the values for *k* and *P* in Table II, E. Nor do these mean pressures vary significantly from the normal control figure of 7.88 ± 0.31 cm. of water (Table II, B and F).

Because of the rising femoral venous pressure throughout the period of gestation, it was necessary in the interests of comparison to divide the arm and femoral pressure determinations into a number of small groups, as has been done in Table I. It will be noted that the ante-partum period has been divided into nine portions and the post-partum period into four.

While there are minor fluctuations in the mean values for antecubital venous pressure determined at various times ante partum and post partum, the range being 6.97 ± 0.39 to 10.75 ± 1.66 cm. of water, none of the group means is significantly different from the normal control value (see Table II, B) for nonpregnant individuals. Although there were a number of rather high individual values for antecubital pressure immediately post partum, it is not possible to demonstrate a significant post-partum elevation when the grouping of values is broadened to forty-eight-hour post-partum periods, as has been done in Tables I and II, B, and in Fig. 1.

The mean values for femoral venous pressure in the various gestational groups show a more or less constant upward trend throughout

TABLE II. SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS FOR ANTECUBITAL AND FEMORAL VENOUS PRESSURE AT VARIOUS STAGES OF NORMAL AND TOXEMIC PREGNANCY, INCLUDING THE PUERPERIUM. PRESSURE IN CM. OF WATER

GROUP	MEAN (1) ± S. E.	NO. OF VALUES IN SAMPLE	MEAN (2) ± S. E.	NO. OF VALUES IN SAMPLE	DIFFERENCE BETWEEN MEANS (1) AND (2)	S. E. OF DIFF.	R (k) *	P†
<i>A. Antecubital Controls (1) vs. Femoral Controls (2)</i>								
All	7.88 ± 0.31	30	11.43 ± 0.64	30	3.55	0.706	5.03	0.000,000.6
<i>B. Antecubital Controls (1) vs. Normal Pregnancy (2)</i>								
5-12 wk. ap.	7.88 ± 0.31	30	7.85 ± 1.02	7	0.03	1.067	0.02	0.984
13-16	7.88 ± 0.31	30	8.07 ± 1.46	7	0.19	1.493	0.13	0.897
17-20	7.88 ± 0.31	30	7.60 ± 1.60	5	0.28	1.630	0.17	0.865
21-24	7.88 ± 0.31	30	8.95 ± 0.73	11	1.07	0.793	1.35	0.117
25-28	7.88 ± 0.31	30	10.75 ± 1.66	4	2.87	1.688	1.70	0.089
29-32	7.88 ± 0.31	30	7.15 ± 0.76	10	0.73	0.821	0.89	0.374
33-36	7.88 ± 0.31	30	6.97 ± 0.39	19	0.91	0.498	1.83	0.067
37-38	7.88 ± 0.31	30	7.11 ± 1.01	9	0.77	1.058	0.73	0.465
39-40+	7.88 ± 0.31	30	7.64 ± 0.39	42	0.24	0.498	0.48	0.631
1-2 days pp.	7.88 ± 0.31	30	8.91 ± 0.69	16	1.03	0.756	1.36	0.174
3-4	7.88 ± 0.31	30	7.94 ± 0.51	16	0.06	0.596	0.10	0.920
5-9	7.88 ± 0.31	30	7.59 ± 0.49	21	0.29	0.579	0.50	0.617
10-20	7.88 ± 0.31	30	7.42 ± 0.96	6	0.46	1.010	0.46	0.646
5-40+ wk. ap.	7.88 ± 0.31	30	7.72 ± 0.23	114	0.16	0.386	0.41	0.682
<i>C. Antecubital Controls (1) vs. Toxemic Pregnancy, Ante Partum (2)</i>								
All	7.88 ± 0.31	30	8.21 ± 0.39	72	0.33	0.498	0.66	0.509
<i>D. Antecubital Normal Pregnancy (1) vs. Toxemic Pregnancy (2)</i>								
25-28 wk. ap.	10.75 ± 1.66	4	9.33 ± 1.61	3	1.42	2.312	0.62	0.535
29-32	7.15 ± 0.76	10	8.11 ± 1.28	9	0.96	1.488	0.65	0.515
33-36	6.97 ± 0.39	19	9.44 ± 1.22	20	2.47	1.280	1.93	0.054 or 0.015 (F) ‡
37-38	7.11 ± 1.01	9	6.88 ± 0.50	9	0.23	1.127	0.20	0.841
39-40	7.64 ± 0.39	42	8.75 ± 0.82	24	1.11	0.908	1.22	0.223
1-2 days pp.	8.91 ± 0.69	16	12.39 ± 1.42	9	3.48	1.578	2.21	0.016 or 0.028 (F)
3-20	7.70 ± 0.31	43	8.59 ± 0.89	17	0.89	0.942	0.95	0.347
5-40+ wk. ap.	7.72 ± 0.23	114	8.21 ± 0.39	72	0.49	0.452	1.09	0.275

*R or (k) = ratio of difference to its standard error.

†P = the probability of the (k) magnitude being exceeded solely through errors of random sampling.

‡P values followed by letter (F) are those computed by Fisher's small sample procedure.

mean of the few remaining post-partum determinations (ten to twenty days) fell within the range of the control mean (11.43 ± 0.64 cm. H_2O). It may be noted in Table II, J, that the mean of all the post-partum femoral pressures in the normally pregnant subjects, as well as the mean of the values from the third to the twentieth day, was significantly less than that for the control group. The post-partum values were, respectively, 9.61 ± 0.27 and 9.38 ± 0.35 cm. of water.

3. *Pregnant Patients With Toxemia.*—Although it would be desirable to group these individuals according to the clinical variety of toxemia (i.e., low reserve kidney, pre-eclampsia, arteriolosclerotic toxemia), there were insufficient numbers of individuals in each category for separate statistical treatment. Furthermore, inspection of the data showed a similar range of values in each toxemic group, so that it seems reasonable to consider these pressures collectively. Since toxemia of pregnancy does not commonly make its appearance in the first half of gesta-

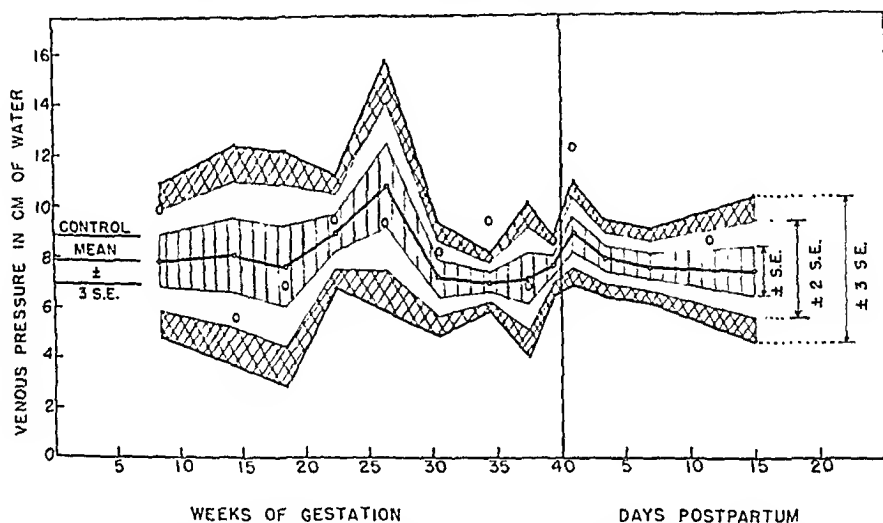


Fig. 1.—Showing the average course of antecubital venous pressure throughout normal and toxemic pregnancy and the immediate puerperium. The heavy central line is drawn through the mean values for normal pregnancy (see Table I) and the three zones on each side of the mean represent areas covered by the mean ± 1 , 2 and 3 standard errors. The superimposed circles indicate mean values for toxemic pregnancies. At the left is shown the range of the mean value for nonpregnant controls.

tion, it was difficult, obviously, to collect sufficient numbers of pressure determinations in the early months to allow statistical analysis of the data. It will be noted in Table I that standard deviations for the toxemia patients were not computed prior to the twenty-fifth week of pregnancy and that the post-partum period was divided into only two instead of four groups. In 55 women with some form of hypertensive toxemia of pregnancy, 208 determinations of venous pressure were made, 149 of them ante partum and 59 post partum. Two patients were observed in two successive pregnancies. Fig. 1 demonstrates that the mean values for antecubital venous pressure in the toxemic individuals fell for the most part within the range of normally pregnant mean plus or minus three standard errors of the mean. The two exceptions were (1) the mean of the values from thirty-three to thirty-six weeks and (2) that of the first forty-eight-hour post-partum period. However, the statistical significance of these differences is open to question when

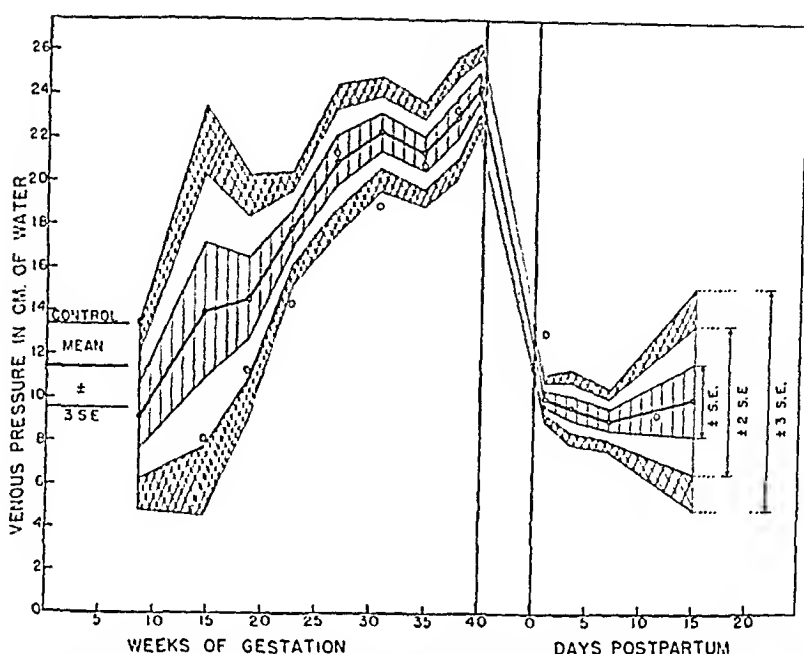


Fig. 2.—Showing the average course of femoral venous pressure throughout normal and toxemic pregnancy and the immediate puerperium. See legend of Fig. 1 for details.

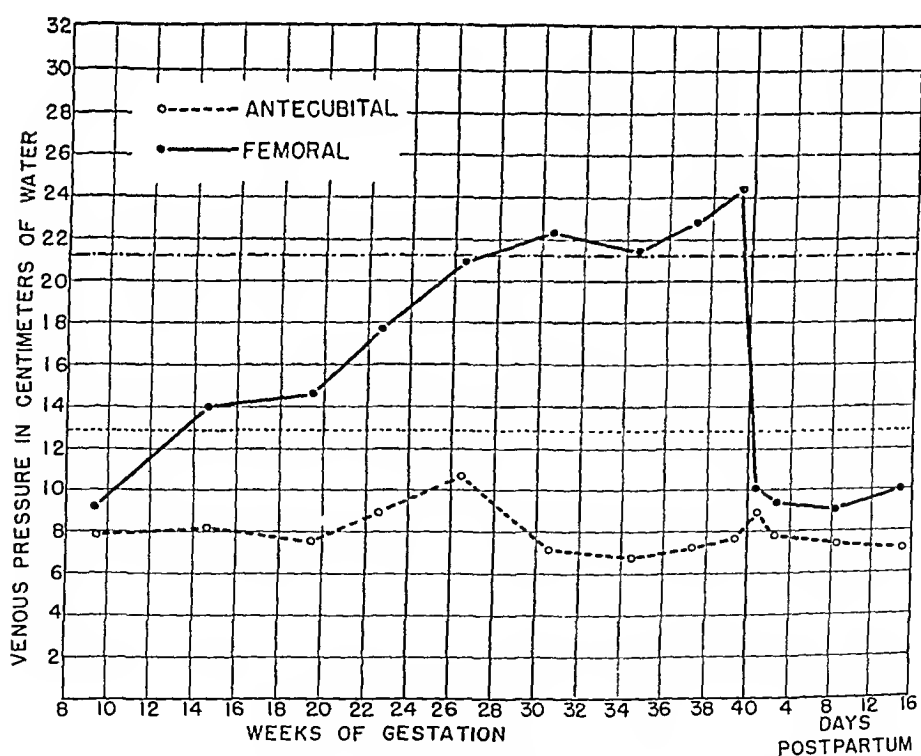


Fig. 3.—Showing the average course of antecubital and femoral venous pressure throughout normal pregnancy and the immediate puerperium, based on 173 antecubital and 227 femoral determinations in 160 pregnancies. The lower straight dotted line represents the upper limit of normal variation for antecubital venous pressure and the upper broken line the same for femoral venous pressure (i.e., control mean + 3 S. D.).

<i>E. Anteubital Normal Pregnancy, Ante Partum (1) vs. Same, Post Partum (2)</i>									
All	7.72 ± 0.23	114	8.03 ± 0.29	59	0.31	0.370	0.84	0.401	
39-40+ wk. ap.	7.64 ± 0.39	42	8.91 ± 0.69	16	1.27	0.972	1.30	0.194	
and 1-2 days pp.									
<i>F. Anteubital Normal Pregnancy, Post Partum (1) vs. Anteubital Controls (2)</i>									
All	8.03 ± 0.29	59	7.88 ± 0.31	30	0.15	0.424	0.35	0.726	
<i>G. Anteubital Tolerias, 39-40+ Wks. (1) vs. Same, 1-2 days pp.</i>									
All	8.75 ± 0.82	24	12.39 ± 1.42	9	3.64	1.640	2.22	0.026 or 0.016(F)	
<i>H. Femoral Controls (1) vs. Normal Pregnancy, Femoral (2)</i>									
5-12 wk. ap.	11.43 ± 0.64	30	9.14 ± 1.45	7	2.29	1.584	1.45	0.147	
13-16	11.43 ± 0.64	30	14.00 ± 3.14	7	2.57	3.207	0.80	0.424	
17-20	11.43 ± 0.64	30	14.60 ± 1.89	5	3.17	1.995	1.59	0.112	
21-24	11.43 ± 0.64	30	17.83 ± 0.88	15	6.40	1.087	5.89	0.000,000,002	
25-28	11.43 ± 0.64	30	21.00 ± 1.15	6	9.57	1.315	7.28	Less than 0.000,000,002	
29-32	11.43 ± 0.64	30	22.29 ± 0.83	12	10.86	1.047	10.37	Less than 0.000,000,002	
33-36	11.43 ± 0.64	30	21.33 ± 0.80	27	9.90	1.024	9.67	Less than 0.000,000,002	
37-38	11.43 ± 0.64	30	22.94 ± 0.94	18	11.51	1.135	10.14	Less than 0.000,000,002	
39-40+	11.43 ± 0.64	30	24.37 ± 0.65	50	12.94	0.912	14.19	Less than 0.000,000,002	
1-2 days pp.	11.43 ± 0.64	30	10.08 ± 0.36	26	1.35	0.734	1.84	0.066	
3-4	11.43 ± 0.64	30	9.64 ± 0.58	21	1.79	0.864	2.07	0.038 or 0.140(F)	
5-9	11.43 ± 0.64	30	9.04 ± 0.48	27	2.39	0.800	2.98	0.0029	
10-20	11.43 ± 0.64	30	10.00 ± 1.73	6	1.43	1.844	0.78	0.435	
<i>I. Femoral Normal Pregnancy (1) vs. Femoral Tolerias Pregnancy (2)</i>									
25-28 wk. ap.	21.00 ± 1.15	6	21.33 ± 2.53	3	0.33	2.778	0.12	0.905	
29-32	22.29 ± 0.83	12	18.88 ± 1.16	8	3.41	1.425	2.39	0.017 or 0.018(F)	
33-36	21.33 ± 0.80	27	20.86 ± 1.60	11	0.47	1.789	0.26	0.795	
37-38	22.94 ± 0.94	18	23.07 ± 0.72	21	0.13	1.183	0.11	0.912	
39-40+	24.37 ± 0.65	50	22.22 ± 0.95	27	2.15	1.150	1.87	0.062	
1-2 days pp.	10.08 ± 0.36	26	13.05 ± 1.46	10	2.97	1.503	1.98	0.048	
3-20	9.38 ± 0.35	54	9.22 ± 0.55	23	0.16	0.652	0.25	0.803	
<i>J. Post-Partum Normal Pregnancy (1) vs. Femoral Controls (2)</i>									
All	9.61 ± 0.27	80	11.43 ± 0.64	30	1.82	0.695	2.62	0.0088	
3-20 days pp.	9.38 ± 0.35	54	11.43 ± 0.64	30	2.05	0.729	2.81	0.0050	

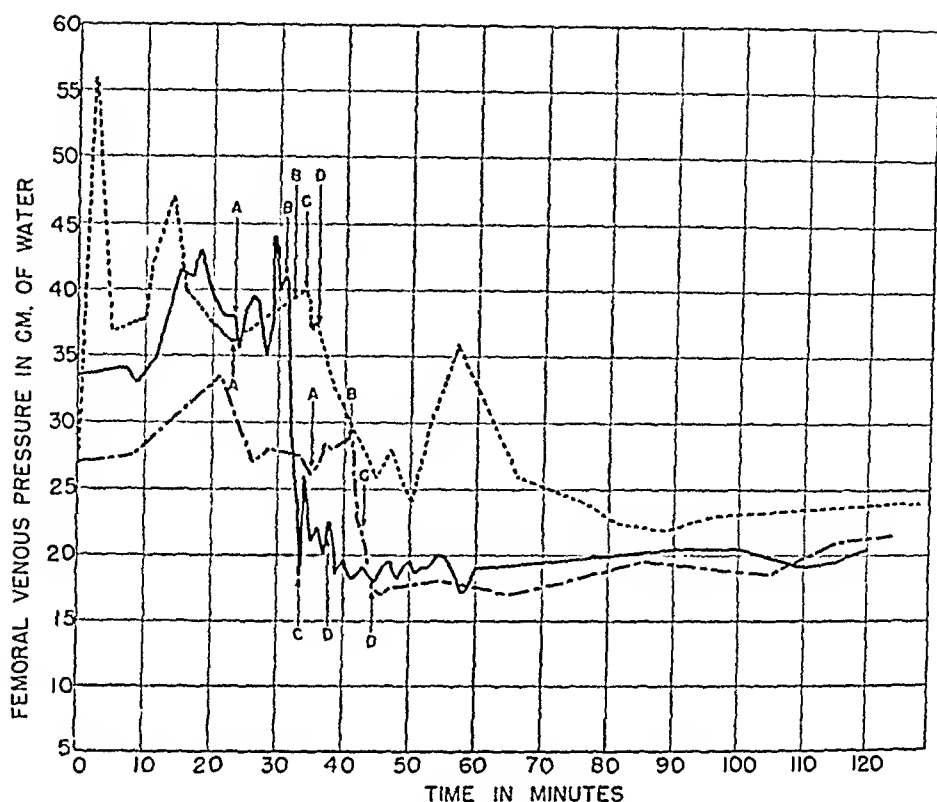


Fig. 4.—Showing the course of femoral venous pressure in 3 patients undergoing delivery by abdominal cesarean section. In each instance, at the point marked A the peritoneal cavity was opened, at B the uterine incision was started, at C the infant was delivered, and at D the placental extraction was completed. (See text for details.)

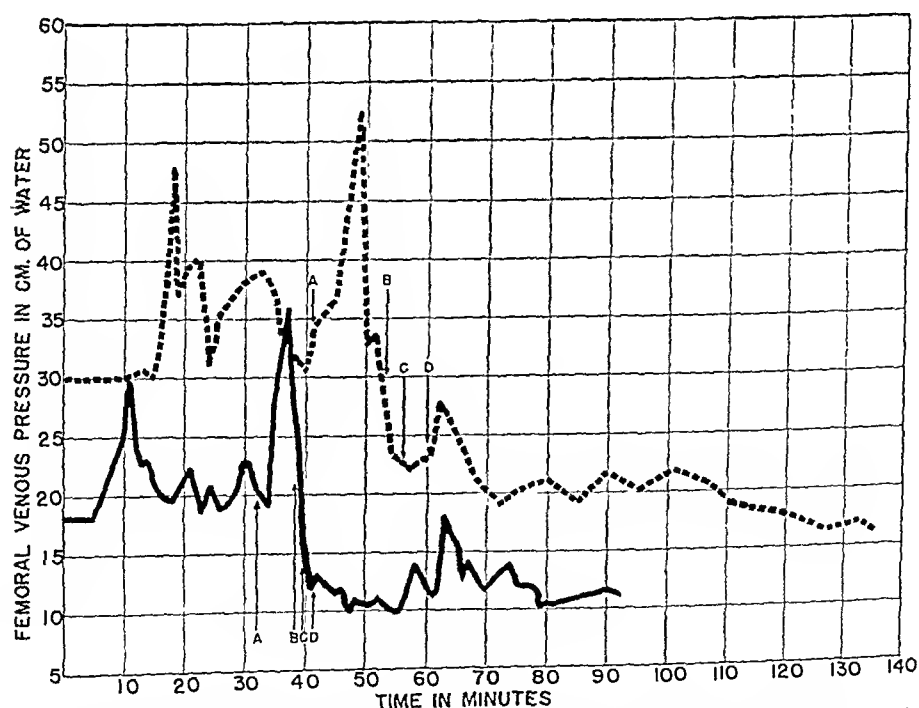


Fig. 5.—Showing the course of femoral venous pressure in two patients undergoing delivery by abdominal cesarean section. (See legend of Fig. 4 for details.)

tested by the usual formulas or even by Fisher's small sample method (see Table II, D). When the mean of the ante-partum toxemia arm pressures is compared with that of the ante-partum arm pressures in the normally pregnant women the difference is not significant (Table II, D, last line), nor is it when the toxemia mean is compared with that of the nonpregnant controls (Table II, C). There is a difference of questionable significance between the toxemia arm pressure in the thirty-nine- to forty-week group and the one- to two-day post-partum group (Table II, G).

In Fig. 2 it may be observed that the mean values for femoral venous pressure fell within the normally pregnant range of means with the exception of the group for twenty-nine to thirty-two weeks and that for the first two days post partum. But in the latter instance the actual difference in means was not statistically significant and in the former it was only questionably so (Table II, I). While graphically (Fig. 2) the mean femoral pressure for toxemic women twenty-one to twenty-four weeks pregnant also falls just below the limit of normally pregnant mean minus three standard errors, little importance can be attached to this occurrence since the mean was derived from only two observations, one of which fell within the normally pregnant range and the other of which was somewhat below it.

4. *Changes in Femoral Venous Pressure During Parturition.*—Determinations of femoral venous pressure were made continuously, values being recorded every one-half, one, two, five, or ten minutes, during the performance of cesarean section. The course of the venous pressure in five such experiments is illustrated graphically in Figs. 4 and 5.

Detailed examination of the protocols for these experiments reveals that femoral venous pressure is exceedingly labile and fluctuates within a wide range during the course of an abdominal operation, particularly when the latter is performed under local anesthesia, as these were. While the use of local anesthesia is obviously advantageous for cesarean section operations, it added somewhat to the difficulties encountered in making continuous observations of venous pressure. In a number of experiments not reported here the results were invalidated by the fact that movements of the patients' lower extremities dislodged the needles from the venous lumina.

The momentary elevations of femoral venous pressure noted in Figs. 4 and 5 occurred for the most part during the early portions of the operations and appeared to be associated with such maternal factors as general muscular rigidity, holding of the breath, straining, talking, and crying. Certain manipulations on the part of the operator also produced transient rises in venous pressure, for example, palpating the exposed gravid uterus and attempting to rotate it within the abdominal cavity, retracting the abdominal walls to expose the uterine appendages, and exerting pressure over the site of the venipuncture (covered by sterile drapes) by inadvertently dropping a hand or instrument at that point. During the course of an oophorectomy in a patient twenty weeks pregnant (not illustrated), it was noted that the manipulations associated with delivery of a large tumor mass through the abdominal incision raised femoral venous pressure to more than 60 cm. of water from a previous level of about 22 cm.

In none of these operations was there any appreciable change in femoral venous pressure at the time the general peritoneal cavity was opened. This was true not only in the five experiments reported here,

than the antecubital and that with one exception the antecubital pressures were within the normal range. Furthermore, all but one of the initial femoral readings may be said to be "elevated" on the basis of the fact that they lie above the range of the control mean ± 3 S. E., i.e., 9.52 to 13.34 cm. of water; and likewise they are above the range of the mean value for 80 determinations in normal post-partum individuals, 8.80 to 10.42 cm. of water. However, if one wishes to judge the normalcy of a single determination by whether or not it falls within the range of control mean + 3 standard deviations, then only five of the femoral pressure readings in these tumor patients fall above the possible limit for controls (21.73 cm. of water), whereas eight of them fall above the same limit for the normal post-partum values (16.73 cm. of water).

It is difficult, of course, to compare these findings directly with the results of venous pressure measurements in pregnant subjects because

TABLE III. ANTECUBITAL AND FEMORAL VENOUS PRESSURES BEFORE AND AFTER OPERATION IN PATIENTS WITH GYNECOLOGIC TUMORS

CASE	AGE YEARS	PRE- OPERA- TIVE DAY	POST- OPERA- TIVE DAY	ANTE- CUBITAL VENOUS PRESSURE CM. WATER	FEMORAL VENOUS PRESSURE CM. WATER	TYPE AND SIZE OF TUMOR
1	48	1	13	8.5 7.5	18.0 10.5	Fibroma ovarii 15 x 12 x 10 cm.
2	71	4	10	4.5 3.5	8.5 4.0	Pseudomucinous cystadenoma ovarii 26 x 22 x 17 cm.
3	44	360		9.5	20.0	Myoma uteri 12 x 11 x 9 cm.
4	48	3	9	3.0 11.0	23.5 9.0	Myomata uteri 22 x 22 x 16 cm.
5	29	5	11	7.5 5.5	11.5 5.0	Myomata uteri 12 x 10 x 9 cm.
6	29	1	1 10	7.5 7.5 3.0	17.0 13.5 10.5	Serous cystoma ovarii and pregnancy, 16 weeks. Cyst 32 x 24 x 12 cm.
7	29	2	11	5.0 6.5	25.0 7.5	Parovarian cyst 25 x 20 x 11 cm.
8	50	-		25.5	29.5	Adenocarcinoma corpus uteri; marked obesity
9	20	1	12	12.0 10.0	26.5 19.0	Pseudomucinous cystadenoma ovarii and pregnancy, 22 weeks. Cyst 20 x 14 x 10 cm.
10	68	2		9.5	15.5	Carcinoma 1. Fallopian tube 13 x 10 x 9 cm.
11	52	1	10	8.5 8.5	15.0 9.5	Serous cystadenoma ovarii, 20 x 17 x 15 cm.
12	44	1	9	12.0 10.0	31.0 13.0	Pseudomucinous cystadenoma ovarii 27 x 24 x 20 cm.

but also in several others in which complete sets of determinations were not obtained because of disruptions in the manometer-vein communications later in the procedures. In the five complete cesarean section experiments the observed changes in femoral venous pressure associated with opening the uterus, rupturing the fetal membranes, extracting the infant, and extracting the placenta were quite variable. The only uniform observation was the lack of appreciable diminution in pressure at the moment of delivery of the placenta. It is difficult to say whether or not any major shift in pressure occurred at the time of placental separation from the uterine wall. In the first place, the precise moment at which separation occurred could not be determined, and second, the time between removal of the infant and delivery of the completely or partially separated placenta was so short that pressure changes attributable to extraction of the fetus undoubtedly masked any additional changes resulting from obliteration of the placental circulation. In the first observation (solid line, Fig. 4) it will be noted that a drop in pressure of 10.5 cm. occurred in the space of thirty seconds during the incision of the uterine wall and rupture of the fetal membranes; then an identical additional drop occurred during the removal of the infant, the manometer meniscus reaching a low point of 18.5 cm. of water at that time. A momentary rise of 7.5 cm. during the clamping of the cord may be attributed to the fact that the infant was resting to some extent on the mother's abdomen during this maneuver. When the child was removed the manometer reading fell again to 21.0 cm. of water and did not vary appreciably during the subsequent removal of the placenta. In the second experiment (lower broken line, Fig. 4) there was a more or less gradual drop in pressure over a period of five minutes from the time the uterine incision was begun until the umbilical cord was clamped, but the entire fall amounted to only 9.0 cm. of water. An additional drop of 1.5 cm. occurred with extraction of the placenta. A third observation (solid line, Fig. 5) showed a femoral pressure drop of 14 cm. of water during the opening of the uterus and delivery of the fetus, the major part of it appearing in connection with the latter process. Delivery of the placenta a minute later was not accompanied by any further diminution in pressure. In the fourth case (dotted line, Fig. 5), there was a drop in pressure of only 4.5 to 5 cm. in the four minutes required for incising the uterus and removing the infant, no further drop with delivery of the placenta, but an additional slow decrease of 5 to 6 cm. during the ensuing seventy-five minutes under general anesthesia. And the fifth case (upper dotted line, Fig. 4) exhibited no appreciable pressure change with removal of either fetus or placenta, although subsequently it fell gradually to a point considerably below the existing level just prior to delivery of the infant. In this particular operation the femoral venous pressure at the end of the procedure was only 4 cm. lower than it had been in the resting state at the beginning of the operation, while in the other four cesarean section observations the differences between initial and final pressure readings were, respectively, 13, 5, 7, and 14 cm. of water.

5. *Venous Pressure in the Presence of Gynecologic Tumors.*—In twelve gynecologic patients with uterine, ovarian, parovarian, and tubal tumors of varying size, both antecubital and femoral venous pressure determinations were made preoperatively and postoperatively. Inspection of the individual values (Table III) for venous pressure reveals that in all instances preoperatively the femoral pressure was higher

em.). When the femoral pressure readings for Cases 5 and 7 are compared with normally pregnant means for the probable fetal age rather than the age by menstrual history they still are lower than the limits of normal mean ± 2 S. E.

Discussion

The average values for venous pressure obtained in the normal control subjects fall well within the range of "normal" previously reported. The determinations on this group of 30 nonpregnant women were made not so much with the purpose of once again defining normal limits of venous pressure as with a view to demonstrating the adequacy of the particular method employed in this study. It should be noted that, while on the average venous pressure was about 3.5 cm. higher in the femoral than in the antecubital vein, this leg-arm relationship was not invariable in individual instances. If the pressure gradient in the venous system which Burton-Opitz^{26, 27} described in the dog exists in the human being, then one might expect that pressure in the femoral vein always would be somewhat above that in an arm vein of the same subject. In fact, McIntire and Turner²⁸ concluded that venous pressure in foot veins of a supine subject invariably was higher than that in the hand veins, since the foot was farther from the heart and thus a higher pressure was required to maintain the gradient of circulation. While this concept was borne out by the statistically significant difference between femoral and antecubital mean values in the present control series, it would appear that certain uncontrollable or perhaps technical factors occasionally enter into the determinations in individual cases so that the expected relationship sometimes is disturbed.

Although Thomson, Reid and Cohen,²⁸ as well as Landt and Benjamin,²⁴ have suggested that venous pressure in the arm is higher in the early months of pregnancy than in the latter months, such a trend is not confirmed by this study, unless one chooses to say, for example, that a mean value of 7.72 cm. of water (at term) is significantly lower than 7.85 or even 8.07 cm. of water (means for five to twelve and thirteen to sixteen weeks). In any event, it may be definitely stated that arm venous pressure in normal pregnancy, despite its minor fluctuations, is at all times well within the normal limits for nonpregnant persons. Statements to the contrary in the literature would seem to be based upon inaccurate and insufficient numbers of observations as well as untenable concepts of the upper limits for normal values.

The observations of femoral venous pressure in normal pregnancy substantiate the statements of previous investigators, notably Runge⁴ and Burwell, Strayhorn and others.³ There would seem to be no doubt that venous pressure in the lower extremities begins to rise above its usual levels by the beginning of the second trimester and continues to increase throughout the remainder of pregnancy, the rate of increase being most marked between the twentieth and thirtieth weeks of gestation. The upward progression of pressure is not constant in all indi-

of differences in size and shape in the tumor masses, as well as differences in weight and location. But in general, it may be said that many of these gynecologic tumors were associated with elevations of femoral venous pressure entirely comparable in magnitude to those seen in the latter months of pregnancy. The sizes of the various tumors which were removed surgically are noted in Table III as three-dimensional measurements in centimeters. From these figures it may be seen that the largest masses were not always found in the persons with the highest venous pressure levels in the lower extremities. In Case 2, for example, a very large pseudomucinous cystadenoma of the right ovary in a thin elderly woman was associated with a femoral venous pressure of only 8.5 cm. of water, while in Case 8 a moderate enlargement of the uterus carried with it a rather tremendous elevation of femoral venous pressure. But the latter apparently cannot be attributed to the uterine mass, since the antecubital venous pressure in this instance also was much above normal levels despite complete lack of other evidences of cardiac decompensation. It is possible that the extreme obesity of the patient was a factor in the disturbance of venous pressure. Finally, it may be pointed out that an appreciable lowering of femoral venous pressure occurred in all of these individuals after removal of the tumors.

6. *The Effect of Intrauterine Fetal Death on Venous Pressure in the Lower Extremities.*—In eight subjects determinations of both antecubital and femoral venous pressure were made after intrauterine death of the fetus. In most instances, of course, it was impossible to determine with any degree of accuracy the exact date of fetal death, so that difficulties arose in attempting to define the duration of gestation in the various cases. Table IV gives the venous pressures, fetal weights, aver-

TABLE IV. ANTECUBITAL AND FEMORAL VENOUS PRESSURES IN PREGNANT WOMEN WITH DEAD FETUSES

CASE	WEEKS PREGNANT BY HISTORY	PROBABLE DURATION ON BASIS OF FETAL WEIGHT WEEKS	ANTE- CUBITAL VENOUS PRESSURE CM. WATER	FEMORAL VENOUS PRESSURE CM. WATER	FETAL BIRTH WEIGHT GRAMS	AVERAGE EXPECTED BIRTH WEIGHT BY HISTORY* GRAMS
1	18	17	8.0	9.5	180	198
2	20	21	12.0	18.0	350	316
3	28	28½	8.0	21.0	1,090	1,045
4	29	28	7.0	21.0	1,070	1,174
5	30	27	13.0	13.5	870	1,323
6	37	33½	6.0	20.5	1,920	2,690
7	39	35½	11.0	11.5	2,370	3,150
8	40	40+	5.0	17.5	3,605	3,405

*Data computed by A. L. Dippel from figures of G. L. Streeter, Contributions to Embryology, vol. XI, Carnegie Institution of Washington, Pub. No. 274, 1920, Table I.

age expected fetal weights for the apparent menstrual ages, and probable durations of fetal lives on the basis of known birth weights. Only three of the femoral venous pressure values fall below the normally pregnant mean pressure minus 3 S. E. as illustrated in Fig. 2, namely, those for Cases 5, 7, and 8. The pressures in Cases 5 and 7 also are beyond the range of normally pregnant mean ± 2 standard deviations (accounting for more than 95 per cent of the variability), but this is not true of the value for Case 8 (which is 17.5 cm. of water, while the normal mean value at term, less twice its standard deviation, is 15.2

lack of rise in arterial blood pressure at the time of occlusion of the shunt-like circulatory mechanism in the placenta. In view of the blood pressure changes observed after closure of arteriovenous fistulas (Reid and McGuire³¹), one might expect such a finding post partum in at least some instances.

Despite the general attractiveness of Burwell's arteriovenous shunt explanation for the alterations in the circulation of pregnant women, the present investigation does not support the notion that the rise in venous pressure of the lower extremities is to any great extent the result of the peculiar placental circulation. In the first place, elevations of femoral venous pressure entirely comparable with those in pregnancy are seen in association with gynecologic tumors. Second, the observations made during cesarean sections, although by no means conclusive, certainly would indicate that the presence of the fetal mass in utero was the major factor in maintaining venous pressure at abnormal levels. Third, observations on patients with dead fetuses in utero suggest that cessation of the placental circulation may not be followed by a demonstrable diminution in venous pressure in the femoral vein. This latter evidence is, of course, open to serious question since one cannot be certain that fetal death necessarily implies occlusion of the intervillous circulation.

Regardless of the precise cause of the elevation in venous pressure, some consideration must be given to the possible effects of such a disturbance. Is the rise in femoral venous pressure late in pregnancy of sufficient magnitude to change capillary pressure and influence the movement of fluid through the capillary walls in a manner conforming to the Starling³² hypothesis? In the light of the observations of Krogh, Landis and Turner,³³ as well as those of Landis and Gibbon,³⁴ one must conclude that a venous pressure of 24 cm. of water (mean femoral venous pressure at term) is sufficient to filter fluid into the tissues. Krogh and others,³³ for example, noted that the rate of filtration was directly proportional to the increase in venous pressure above an average venous pressure of 17 cm. of water, while Landis and Gibbon³⁴ found this to be true above an average pressure of 12 cm. of water. However, at venous pressures in the neighborhood of 20 to 25 cm. of water the actual quantity of fluid filtered per minute is not particularly great, and it seems unlikely that this increase in filtration would overburden the mechanisms for the removal of tissue fluid. Furthermore, in the presence of continued venous congestion, some force, presumably tissue pressure, diminishes the power of a given venous pressure to filter fluid from the blood into the tissue spaces. For example, in the experiments of Landis and Gibbon,³⁴ when the filtered fluid amounted to 1.0 c.c. per 100 c.c. of arm, filtration was decreased approximately 0.033 c.c. per minute per 100 c.c. of arm, a change which corresponded to the effect of lowering venous pressure by 10 cm. of water. The accumulation of 1.5 c.c. of fluid per 100 c.c. of tissue resulted in the rapid

viduals on bed rest; many of these show minor decreases in femoral venous pressure after some days or weeks in bed, despite advancing pregnancy, but average figures demonstrate a continuous upward trend. It is likely that the apparent slight drop in the mean value between thirty-three and thirty-six weeks may be explained on the basis of the relatively small number of observations in the preceding group, tending to make its mean somewhat too high. It should be noted, however, that while the mean femoral vein pressure in the last two weeks of pregnancy was more than double that of the nonpregnant control subjects, it was less than 3 cm. above the limit of control mean plus three standard deviations. In other words, although individual rises in femoral venous pressure are striking and unmistakable, and although the mean values early and late in pregnancy are clearly far apart, still the average value at term cannot be looked upon as enormously elevated by comparison with the possible range of normal variation in this measurement.

Granted that there is a real elevation of venous pressure below the level of the pregnant uterus, two questions present themselves for argument. First, what is the reason for the abnormal pressure, and second, is the pressure of sufficient magnitude to cause disturbances in the normal circulatory mechanism? Burwell and his co-workers¹⁻³ have pointed out that the pressure exerted by the blood in any vein is dependent partly on the resistance to its outflow and partly on the amount and the pressure of the blood flowing in. They admit that their observations of venous pressure in patients with pelvic tumors strongly suggest that an important factor in the rise of venous pressure is interference with venous flow by the pressure of the enlarging uterus. But at the same time they apparently feel that the factor of increased flow into the veins draining the uterus (Runge) may be equally operative in producing elevations of venous pressure. Their evidence in favor of the latter concept is two-fold: (1) observations in pregnant bitches showing that femoral venous pressure fell when the gravid uterus was lifted from the abdomen so that it no longer pressed upon the great veins, but that even then the pressure usually remained above the pressure in the jugular vein; (2) Spanner's²⁹ anatomic description of the vascular system of the placenta, indicating that arteries connect with veins through large vascular spaces and without the interposition of arterioles or capillaries, a structure, then, similar in many respects to a simple arteriovenous shunt. It should be mentioned here that Stieve³⁰ has taken exception to that portion of Spanner's work dealing with the return venous flow from the placenta, although there is no evidence that the description of the manner in which terminal arteries empty into intervillous spaces is incorrect.

While the arteriovenous shunt circulatory changes may quite adequately explain the vast majority of the phenomena observed during pregnancy, there is as yet no adequate explanation for the apparent

this regard that edema appearing in warm weather is undoubtedly in part due to the accelerated accumulation of tissue fluid because of the increase in temperature of the part involved. This effect of temperature on rates of filtration was clearly shown in the experiments of Landis and Gibbon, where, for example, the rate of filtration at 44° C. was twice as great as that at 14° C.

The recent work of Linton and others⁴⁰ on the effect of venous occlusion on arterial inflow to an extremity raises the question of whether blood flow in the lower extremities of pregnant women may be appreciably increased because of venous congestion. The congestion in pregnancy, of course, is not intermittent, as it is when employed therapeutically. Abramson, Flachs and Pierst,⁴¹ however, have reported that they could demonstrate no significant change from the normal in blood flow in the legs of pregnant women, although some of their subjects seem to show a trend toward an increased flow during the last lunar month of gestation.

The data for the toxemia patients in the present study refute statements in the literature to the effect that antecubital venous pressure is elevated in toxemia of pregnancy. As has already been pointed out by Thomson, Reid and Cohen,¹⁸ the level of the venous pressure in toxemia in no way correlates with the severity of the disease, the degree of edema or the height of the arterial blood pressure. This result one might have anticipated in view of the many previous reports on the absence of correlation between arterial and venous blood pressures.^{17, 42-44}

The statistically significant difference between the mean femoral venous pressure post partum and the mean for the normal control subjects requires some comment. At least two possible explanations for this observation have suggested themselves. The first is that these subjects were on continuous and absolute bed rest. It is conceivable that prolonged assumption of the supine posture tends to bring the femoral venous pressure to a level somewhat below the average for persons who have only a few minutes previously abandoned the upright position, with its known increments in venous pressure in the lower extremities. Second, certain observations not reported here point to the fact that the slight sagging of the bed at the site of the buttocks may be a factor in depressing venous pressure 2 to 3 cm. of water in the femoral vein. On theoretical grounds, it would seem that a lowering of this part of the body would tend to raise femoral venous pressure when the manometer is kept at the same level as that used for the arm determination. However, it was repeatedly observed that femoral venous pressure in subjects lying on a firm, perfectly horizontal examining table was somewhat higher than that in persons lying in bed. In an attempt to discover the effect of lowering the general region of the buttocks, subjects were placed on a delivery table with a depressable foot section. Supporting the feet and legs distal to the table, and the head and chest on the stationary portion, it was possible to lower the pelvic region below the

removal of fluid even with a venous pressure of 20 cm. of water. Additional evidence that venous pressures of 20 to 25 cm. of water are not particularly effective filtering pressures is brought out in the study of Landis, Jonas, Angevine and Erb,³⁵ where filtration was measured indirectly by determining cell volume, hemoglobin and erythrocyte counts. While loss of fluid from the blood was conspicuous at venous pressures of 40 to 80 mm. of Hg, it could barely be detected at a venous pressure of 20 mm. Hg (27 cm. of water).

Available data from direct measurements seem to show that tissue pressure is not always significantly elevated by prolonged venous congestion and that even in edema the values are not nearly as high as would be expected (Burch and Sodeman³⁶). But it should be remembered that these data refer only to subcutaneous and intracutaneous pressures. Wells, Youmans and Miller,³⁷ on the other hand, have measured tissue pressure in muscle as well as in the superficial tissues; their interest centered mainly on the leg because of the well-known paradox of the failure of edema to develop in legs of normal individuals on prolonged quiet standing. It would appear that in the tightly covered muscles, as the soleus and anterior tibial, tissue pressure starts at a high level and increases quite rapidly to values which are of the magnitude required by Starling's hypothesis to oppose effectively further filtration (50 cm. of water, or higher, in some experiments). In more loosely covered muscles, such as the gastrocnemius, intramuscular pressure remains at lower levels which probably are ineffective in stopping filtration; the same seems to be true for the skin. Because of this latter relationship, the leg volume may continue to increase during quiet standing at a low residual rate (maximum time of observation was 2.5 hours). These workers feel that it is not necessary to postulate extensive lymphatic drainage from the congested area to account for the retardation in the rate of swelling of the leg, as suggested by Beecher.³⁸

The experiments of Drury and Jones³⁹ demonstrated that palpable edema in the leg did not occur until the amount of collected tissue fluid had increased the limb volume by 8 per cent. If this be true, then, in the light of what has just been said about filtration rates at low venous pressures, it seems quite unlikely that the venous pressure existing in the femoral vein in the latter part of pregnancy could lead routinely to the production of clinical, pitting edema. And this is borne out, of course, by the fact that while all pregnant women at term exhibit elevated femoral venous pressure, not all have pitting edema of the lower extremities. On the other hand, it must be concluded that the increased venous pressure in pregnancy does tend to promote the accumulation of tissue fluid in the lower extremities, and thus set up sub-clinical degrees of edema which are easily and quickly thrown over into detectable edematous states by some further derangement of the normal mechanism for fluid exchange. It should be remembered in

Patients with large pelvic tumors exhibit elevations of femoral venous pressure entirely comparable to those seen late in pregnancy. These pressures return to normal values after removal of the tumor masses.

Pregnant women with dead fetuses in utero appear, for the most part, to have elevations of femoral venous pressure of a magnitude similar to those seen in normal pregnancies with living fetuses.

Reasons are presented for thinking that the level of venous pressure observed in the lower extremities, while admittedly abnormal, is not sufficiently high to produce obvious pitting edema in all pregnant women, although it probably promotes subclinical degrees of edema routinely.

The present study does not suggest that the elevation of femoral venous pressure in pregnancy is to any great extent the result of an arteriovenous-shuntlike mechanism operating in the placenta. The abnormal venous pressure appears to be the result of obstruction to venous return by the pregnant uterus.

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general level of the rest of the body. When this was done, with continuous observation of femoral venous pressure, it was found that the femoral pressure invariably fell as the buttocks were depressed and rose again to the initial level when the buttocks were restored to their original position. I have no adequate explanation for this apparently paradoxical phenomenon. When the entire body was tilted to a semi-erect posture, the expected change (Mayerson and Bureh⁴⁵) in femoral pressure occurred, that is, a marked rise, and conversely, in the Trendelenburg position, femoral venous pressure dropped to very low levels.

Summary and Conclusions

By a direct method, 757 determinations of venous pressure were made in 255 subjects. Three hundred and forty-five determinations were made in the antecubital vein and 412 in the femoral vein. The subjects were normal nonpregnant females, normally pregnant women, normal postpartum patients, pregnant women with hypertensive toxemias, and gynecologic patients with pelvic tumors. In some instances determinations were made during the course of operative delivery by abdominal cesarean section. Accepted statistical formulas were employed in the analysis of the results.

In 30 normal, nonpregnant women the average antecubital venous pressure in the supine posture was 7.88 ± 0.31 cm. of water and the average femoral venous pressure was 11.43 ± 0.64 cm. of water.

Antecubital venous pressure in normal pregnancy is not significantly different from that in the nonpregnant state and shows no particular trends during the course of pregnancy. Femoral venous pressure in normal pregnancy begins to rise in the early part of the second trimester, rises rather rapidly between the twentieth and thirtieth weeks of gestation, then somewhat more slowly to reach an average peak value at term of approximately 24 cm. of water. It falls quickly after delivery to nonpregnant levels and apparently lies somewhat below the average control level during the puerperal period of bed rest.

Patients with toxemia of pregnancy have antecubital and femoral venous pressures within the range of those for normally pregnant persons.

During the course of abdominal cesarean section, femoral venous pressure usually shows a marked decline after removal of the fetus from the uterine cavity, and is not appreciably affected by opening the peritoneal cavity, incising the uterine wall, or delivery of the placenta. Because of the short time interval between delivery of the fetus and of the placenta, such observations have not been of great value in differentiating between that increment of venous pressure resulting from the presence of the fetal mass and enlarged uterus and that owing possibly to a transfer of high arterial pressures at the placental site (arteriovenous shunt effect).

TABLE I. THYROTOXICOSIS AND PREGNANCY (INCIDENCE IN REPORTED SERIES)

AUTHOR	YEAR	REGION	SERIES OF PREGNANCIES	CASES HYPER-THYROIDISM IN PREGNANCY	PER-CENTAGE INCIDENCE
Yoakam	1928	Michigan	937	35	3.7
Wallace	1933	New York	11,571	9	0.07
Portis and Roth	1939	Illinois	1,000	14	1.4
Javert	1940	New York	23,439	18	0.076
McLaughlin and McGoogan	1942	Nebraska	6,112	19	0.3
Total			43,059	95	0.22
AUTHOR	YEAR	REGION	SERIES OF THYROIDECTOMIES	NO. PATIENTS PREGNANT	PER-CENTAGE INCIDENCE
Mussey	1926	Minnesota	7,228	42	0.5
Clute and Daniels	1929	Massachusetts	3,678	18	0.41
Frazier and Ulrick	1932	Pennsylvania	1,350	38	3.2
Bram	1936	Pennsylvania	4,000	12	0.3
Total			15,256	110	0.72

pregnancy after the onset of the disease was rare. Bram studied the menstrual histories of 4,000 patients with Graves' disease, finding it normal in 31 per cent, delayed or irregular in 43 per cent, amenorrhea present in 24 per cent, and menorrhagia in 2 per cent.

In normal pregnancy there occurs a very definite alteration in the function and balance of the ductless gland system and this is further affected by the development of hyperthyroidism.

The normal variations in the basal metabolic rate during and immediately following pregnancy have been rather extensively studied by a number of investigators (Sandiford and Wheeler, Hanna, Cornell, Enright, Cole, and Hitchcock, Root and Root, and Hughes). All of these observers are essentially in agreement that the basal metabolic rate remains normal during the first four or five lunar months of pregnancy, gradually rising during the last three or four months to reach an average increase of 20 to 25 per cent above the normal at term. Following delivery the basal metabolic rate promptly falls within ten days to a normal level but is usually a little below the readings obtained during the fourth and fifth lunar months of pregnancy. This elevation in the basal metabolic rate is resultant from the presence of an increasing mass of protoplasmic or fetal tissue, to a lesser extent an increase in maternal structure, and to simple hypertrophy and hyperplasia of the thyroid gland. It tends to be much more apparent in young girls than in mature women. Plass and Yoakam have observed that women with palpable thyroid glands show a greater tendency to high basal metabolic rates during pregnancy. Those with small colloid or adenomatous glands developed an average increase of 35 per cent in their basal metabolic rate, while those with larger colloid goiters had an elevation of approximately 50 per cent. Yoakam, Hinton, and Hanna have each observed enlargement of the thyroid gland in approximately 50 per cent of pregnant women under observation confirming the presence of an increased thyroid mass during these months, particularly noticeable in the thyroid belts.

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HYPERTHYROIDISM COMPLICATING PREGNANCY

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THE problems presented by hyperthyroidism complicating pregnancy have been of great interest to surgeons and obstetricians alike during recent years. During the ten-year period from 1932 to 1942 a total of 6,112 obstetric patients were delivered in the University Hospital or on the out-call service under the supervision of the obstetric staff. Thyrotoxicosis was observed as a complication of pregnancy in 19 women, an incidence of 0.3 per cent. An analysis of these 19 patients was undertaken, together with a review of the experience of others, in an effort to determine the most satisfactory method of treatment.

The incidence of thyrotoxicosis complicating pregnancy varies markedly in different sections of this country and in various parts of the world. In general those sections in which goiter is endemic will see many more cases than those in which thyroid disease is less commonly encountered. In Table I is listed the occurrence of hyperthyroidism and pregnancy as observed in several sections of America. From this it may be assumed that hyperthyroidism will be present or develop in approximately 0.22 per cent of all women during pregnancy. It is interesting to note that the incidence of pregnancy in established thyroid disease is over three times as high as the incidence of thyroid disease developing during pregnancy. In England Gardiner-Hill has reported a series of 115 women with hyperthyroidism during pregnancy, of whom 89 were classified as typical Graves' disease. He concluded that pregnancy occurred in about 50 per cent of those patients with primary exophthalmic goiter in which it was possible but noted that more than one

rates during the first trimester of pregnancy has reduced the incidence of late toxemias by 50 per cent, but warns that medication must be given early in pregnancy.

There is no unanimity of opinion in the literature on the effect of hyperthyroidism upon the unborn child, excepting an occasional reference to fetal abnormalities. Dean reports a mother with simple goiter who in succession was delivered of two anencephalic monsters, each with enlarged thyroids. Subsequently when placed on iodine a normal male child was delivered. Warren and Shpiner observed a young woman with a very toxic diffuse goiter who was operated upon in two stages during the third and fifth months of pregnancy. The patient aborted identical twins three weeks after the second operation, the cord to one of the twins having been obstructed in utero. This twin showed a typical hyperplastic thyroid and the authors conclude that this fetus mirrored the thyroid status of the mother at the time of operation, mechanical factors having altered the character of the blood supply rendering the fetal thyroid inert to change.

Report of Cases

The 19 patients here reported with hyperthyroidism complicating pregnancy averaged 29 years of age (Table II). The oldest was 40, the

TABLE II. THYROID DISEASE COMPLICATING PREGNANCY

Total deliveries 1932-1942	6,112
Thyroid disease complicating pregnancy	19
Oldest patient	40
Youngest patient	19
Average age	29
White patients	18
Colored patients	1

youngest 19. Only one in the series was observed in the colored race which corresponds in general to the ratio of colored patients seen on the obstetric service.

Only two patients were seen with hyperthyroidism during their first pregnancy (Table III). The 19 patients comprising this series had had a total of 46 previous pregnancies, or an average of 2.4 children.

TABLE III. PREVIOUS DELIVERIES IN PATIENTS ADMITTED WITH THYROID DISEASE COMPLICATING PREGNANCY

PATIENTS	PREVIOUS PREGNANCIES
2	0
2	1
2	2
4	3
3	4
1	5
2	6
1	7
1	8
1	10
Total 19	46

In experimental studies with guinea pigs, Hewitt and Van Lier were unable to demonstrate any true increase in the thyroid weight:body weight ratio during pregnancy; either early, late, or during the post-partum period. Soule demonstrated experimentally a substance in the blood serum of pregnant women capable of reducing the liver glycogen level in the mouse with a resultant increase in the level of circulating thyroid hormone. He concluded that an actual physiologic hyperfunction of the thyroid gland during pregnancy was responsible for the increase in the thyroid hormone.

These findings make it extremely important that the clinician differentiate between thyroid hyperplasia and true thyrotoxicosis during pregnancy.

Enright, Cole, and Hitchcock have shown that the administration of iodized salt during pregnancy furnishes an adequate amount of iodine and prohibits in part the usual elevation in the basal metabolic rate during the third trimester. Phatak, Zener, and David have confirmed these observations, pointing out that the supplemental iodine is utilized principally during the third trimester of pregnancy when the blood iodine level tends to decrease in those patients from whom iodine medication is withheld. Hughes¹⁸ reports two patients with signs of hyperthyroidism developing during the third trimester of pregnancy. Both had thyroidectomies following delivery and in neither case was the tissue pathologically as active as anticipated. He suggests that the presence of true hyperthyroidism can best be judged and evaluated during the first trimester of pregnancy when thyroid activity is usually within normal limits. In one of our patients (Case 14) subjected to thyroidectomy during the third month of pregnancy, the excised tissue showed only thyroiditis with no evidence of activity, casting some question on the preoperative diagnosis of exophthalmic goiter.

Clute and Daniels in an extensive experience with thyroid disease state that pregnancy does not appear to be a cause of primary hyperthyroidism and conclude that "we have never seen anything occur in any woman with hyperthyroidism and pregnancy which does not commonly occur in nonpregnant thyroid cases of that type."

There is good evidence that the toxemias of pregnancy occur more frequently in those cases complicated by thyroid disease.

Javert observed some degree of toxemia in 76 per cent of his 18 cases of associated hyperthyroidism and pregnancy in contrast to an incidence of 7.6 per cent in noncomplicated cases, raising the question of a common etiology. Colvin and Bartholomew noted the frequent occurrence of toxemia in young primiparas with normal or subnormal basal rates and a high blood cholesterol during the first trimester of pregnancy. With the development of a true toxemia, the basal metabolic rate promptly rises with an associated fall in the blood cholesterol; both figures returning to normal amounts during the puerperium. These authors advise the administration of thyroid extract with a restriction of cholesterol-containing foods to prevent the late toxemias of pregnancy. Hughes¹⁹ reports that the administration of thyroid to patients with low basal

Every one of this series of patients had been conscious of the presence of a goiter prior to the onset of pregnancy during which thyrotoxicosis became a real factor. Actual symptoms of hyperthyroidism appeared for the first time during pregnancy in only three cases, the remaining 16 patients having definite evidence of thyrotoxicosis prior to conception. In Table IV is noted the effect of previous and the present pregnancies on the thyroid status. Wallace observed that pregnancy influenced existing thyrotoxicosis in one of three ways:

1. It may definitely improve it in a fair percentage of cases, occasionally permanently.
2. It may neither ameliorate nor aggravate the condition.
3. It may markedly increase the thyrotoxicosis.

Bram found in his series of cases that in 30 per cent the syndrome was not aggravated by pregnancy. In the remaining 70 per cent the thyroid disease was made worse and in 15 per cent spontaneous abortion occurred.

In our series the thyrotoxicosis was definitely aggravated by the pregnancy in 13 cases (74 per cent), slightly increased in four cases (21 per cent), and not affected in one case (5 per cent). Five patients were admitted during the first trimester of pregnancy, 6 during the second and eight during the third. On the basis of clinical toxicity, the patients were divided into three groups, 31 per cent being considered mildly toxic, 42 per cent moderately toxic and 27 per cent acutely ill with marked thyrotoxicosis.

Exophthalmic goiter was the type of thyroid disease present in 10 of the 19 patients the remaining 9 having adenomatous goiter with secondary hyperthyroidism. In any series of patients with hyperthyroidism complicating pregnancy, exophthalmic goiter is inevitably the most common type encountered because of the age of the patients. The average age of our 9 patients with adenomatous goiter and hyperthyroidism was 32 years, while the 10 women with exophthalmic goiter averaged 27 years of age. Mussey, Plummer, and Boothby²⁴ have reported that 70 per cent of all patients with exophthalmic goiter are under the age of 40, while approximately the same percentage of patients with adenomatous goiter and hyperthyroidism are over 40 years of age.

A study of the variation in weight experienced by this group of patients was undertaken. Adequate data were available in 10 patients, of whom 6 gave a history of weight loss and 4 had gained. An evaluation of the loss of weight in these 6 cases, averaging 20 pounds, is difficult since all were observed between the second and fifth months of their pregnancy. The thyrotoxicosis present was undoubtedly a factor in their loss in weight, but the nausea and vomiting so frequently seen in these pregnant women with hyperthyroidism must be considered an associated cause. None of the 4 patients with a known gain in weight had increased over that amount which might be expected for their stage in pregnancy.

A correlation of the blood pressure, pulse, basal metabolic readings, and period of gestation in this series of 19 cases is outlined in Table V. Considering a systolic pressure of 140 and a diastolic of 90 as the top limit of normal, 9 patients in the group might be considered to have hypertension. At rest under basal conditions 10 of the 19 patients had a pulse rate of 100 or above after admission to the hospital. The basal metabolic readings were quite difficult to evaluate unless considered with the clinical picture, period of gestation, and history of previous iodine

TABLE IV. EFFECT OF PREVIOUS AND PRESENT PREGNANCY ON THYROID DISEASE

CASE	DURATION GOITER	NO. PREVIOUS PREGNANCIES	ONSET SYMPTOMS	MONTH GESTATION ON ADMISSION	EFFECT PREGNANCY ON THYROID DISEASE	TOXICITY ON ADMISSION
1	9 years	5	Increasing each pregnancy	7	Increasing toxicity	3 plus
2	12 years	4	1 year ago	3	Increasing toxicity	2 plus
3	5 years	1	2 years ago	4½	Increasing toxicity	2 plus
4	5 years	8	5 years ago increasing	9	Increasing toxicity	2 plus
5	6 years	3	Increasing 5 months	8	Increasing toxicity	2 plus
6	8 years	7	3 months ago	8½	Increasing toxicity	3 plus
7	8 years	1	7 years ago thyroidectomy	7	Increasing toxicity	2 plus
8	20 years	4	6 years ago recurrence	7	Increasing toxicity	3 plus
9	1 year	0	Increasing each pregnancy	5	Increasing toxicity	2 plus
10	6 years	10	3 months ago	1	Increasing toxicity	1 plus
11	2 years	2	1 year	3	Increasing toxicity	2 plus
12	18 months	2	2 years	4	Increasing toxicity	1 plus
			1 year		No increase	
13	8 years	6	8 years ago thyroidectomy	9	Increasing toxicity	2 plus
14	8 years	6	7 years ago recurrence	2	Slight increase	1 plus
15	2 years	3	Increasing 6 years	2	Increasing toxicity	1 plus
16	1 year	0	Increasing 2 years	4	Increasing toxicity	3 plus
17	4 years	3	Increasing 1 year	4	Slight increase	1 plus
18	20 years	3	Increasing 4 months	6	Slight increase	1 plus
19	8 years	4	Gradual increase	8	Slight increase	2 plus
			Increase 2 years			

therapy. The highest basal metabolic rate in the group was plus 70 with the more toxic patients ranging from plus 40 to plus 65. Eight patients had received no therapy for their thyrotoxicosis prior to their hospital admission, while an additional group of 8 had been on Lugol's solution for periods varying from two months to three years. Two patients had previously undergone thyroidectomy seven years before admission with a recurrence in each instance. One of these subsequently had radium therapy elsewhere for her thyrotoxicosis without benefit. X-ray therapy had been employed in one case for the treatment of the hyperthyroidism without improvement prior to conception.

Of the 8 patients admitted to the University Hospital in the last trimester of pregnancy, 5 (62.5 per cent) exhibited the signs of toxemia of pregnancy in one or another of its various forms. Only 1 of the 5 patients presented the classical triad of hypertension, edema, and albuminuria. This was in 1 of the 2 cases of exophthalmic disease. The other 4 patients had hypertension and edema but no albuminuria. These 4 cases occurred in the six instances of adenomatous disease. The true incidence of toxemia occurring in thyroid disease in our series of 19 cases was 26.2 per cent which is considerably lower than that of Javert who reported 76 per cent incidence in 18 cases.

The therapeutic measures employed in this group of 19 patients are outlined in Table VI. Eighteen of the 19 cases have been followed through their pregnancy and for a variable period afterwards. A live baby was obtained in all but one instance and one mother was delivered of twins. There were two maternal deaths in the series.

Eleven patients were treated conservatively with rest, Lugol's solution, and sedatives. In nine instances delivery was uneventful, in one section was done, and the eleventh is now in the hospital in the eighth month of her pregnancy. The 11 babies delivered were all normal excepting two, who were premature but survived. Thyroidectomy has been done in 4 cases since delivery with a satisfactory result in each instance, and will be done during the post-partum period in the one case now in the hospital approaching term. Four of the remaining 6 patients treated conservatively have been followed and in every instance the thyrotoxicosis has subsided and the patients are clinically well. Efforts to trace two patients have been unsuccessful, but at their dismissal following delivery, thyroidectomy was not considered necessary.

Surgical treatment of the hyperthyroidism during pregnancy was advised and carried out in seven cases. Five patients successfully underwent subtotal thyroidectomy; two in the third, one in the fourth, one in the fifth, and one in the sixth month of pregnancy. Each mother subsequently delivered a normal, live child, and has remained well to date, although one has a basal metabolic rate of -41 with mild hypothyroidism. The remaining two desperately ill patients were treated by staged placentation in the seventh and eighth months of pregnancy. One was delivered of a normal child at term while in the second instance the baby was stillborn and macerated. A subtotal thyroidectomy was done during the post-partum period in one case with an excellent result and a subsequent pregnancy has been completed without incident. Thyroidectomy following delivery was planned in the second case, but the patient died of a pulmonary embolus on the fourteenth post-partum day.

The other maternal death in this series of 19 cases occurred in a 34-year-old colored woman admitted at term with myocarditis and an

TABLE V. CORRELATION OF BLOOD PRESSURE, PULSE, BASAL METABOLIC RATE, AND PERIOD GESTATION IN PATIENTS ADMITTED WITH HYPERTHYROIDISM AND PREGNANCY

CASE	AGE	BLOOD PRESSURE	PULSE	B.M.R.	MONTH GESTATION	PREVIOUS TREATMENT	TYPE THYROID DISEASE
1	28	155/0	130	Plus 70	7	None	Adenomatous with hyperthyroidism
2	40	118/80	100	Plus 45	3	None	Adenomatous with hyperthyroidism
3	20	135/75	100	Plus 42	4½	Iodine 3 years	Adenomatous with hyperthyroidism
4	34	160/50	100	?	Term	Iodine 3 years	Adenomatous with hyperthyroidism
5	24	160/90	140	Plus 25	8	None	Adenomatous with hyperthyroidism
6	31	138/70	?	Plus 32	8½	Iodine 3 months	Adenomatous with hyperthyroidism
7	32	200/110	140	Plus 65	7	Thyroidectomy 7 years ago Radium 3 years ago rec.	Exophthalmic goiter
8	40	178/90	160	Plus 57	7	None	Adenomatous with hyperthyroidism
9	27	128/64	84	Plus 29	5	None	Exophthalmic goiter
10	37	145/100	80	Plus 17	1	None	Exophthalmic goiter
11	24	145/60	90	Plus 40	3	X-ray therapy 6 months previous. No benefit	Exophthalmic goiter
12	28	104/50	70	Plus 30	4	Iodine 2 months	Exophthalmic goiter
13	26	120/70	90	Plus 35	9	Thyroidectomy 7 years ago	Exophthalmic goiter
14	27	125/75	88	Plus 17	2	Recurrent 6 years ago	Exophthalmic goiter
15	26	140/85	90	Plus 20	2	Iodine 2 months	Exophthalmic goiter
16	19	160/75	110	Plus 69	4	None	Exophthalmic goiter
17	25	134/76	100	Plus 12	7	Iodine 6 months	Exophthalmic goiter
18	38	122/78	96	Plus 29	6	Iodine 3 months	Adenomatous with hyperthyroidism
19	33	162/90	110	Plus 62	8	Iodine 3 months	Adenomatous with hyperthyroidism

TABLE VII. TREATMENT REPORTED CASES HYPERTHYROIDISM COMPLICATING PREGNANCY

AUTHOR	YEAR	CASES	TYPE		CASES SURGERY BEFORE DELIVERY			PATIENTS TREATED CONSERV.	MIS-CARRIAGES	THERAPEUTIC ABORTIONS	MORTALITY		THYROIDECTOMY AFTER DELIVERY
			N. G.	T. A.	N. G.	T. A.	TOTAL				CHILD	MOTHER	
Robinson	1922	15	15	0	0	0	0	15	0	0	0	0	0
Strouse and Daly	1926	61	0	0	0	0	0	61	0	0	0	0	Several
Hynnan and Kessel	1927	9	0	0	0	0	0	9	1	0	0	0	0
Yoakum	1928	35	0	0	0	1	1	34	0	0	0	0	0
Clute and Daniels	1929	18	16	2	0	0	15	3	1	0	0	0	0
Plummer, et al.	1929	42	32	10	25	8	32	10	2	0	0	0	3
Fahrni	1930	14	11	3	11	3	14	0	2	0	2	0	0
Mussey and Plummer	1931	41	29	12	22	9	31	10	0	0	1	0	1
Lahey	1931	15	0	0	0	0	15	0	0	0	0	0	0
Trazier and Ulrick	1932	38	0	0	0	0	7	31	0	0	1	0	0
Bothe	1933	10	0	0	0	0	5	5	0	0	0	0	0
Wallace	1933	9	0	0	0	0	0	9	1	0	0	0	0
Portis and Roth	1939	14	0	0	0	0	2	12	0	3	3	0	0
Mussey	1939	66	43	23	29	19	48	18	0	1	1	0	0
Total		387			29	19	170	217	7	4	11	0	7

TABLE VI. TREATMENT OUR SERIES PATIENTS WITH HYPERTHYROIDISM COMPLICATING PREGNANCY

CASE	TYPE	TOXICITY	IMMEDIATE TREATMENT	SURGERY BEFORE DELIVERY	LABOR	SURGERY FOLLOW- ING LABOR	END RESULTS
1	T. A.	3 Plus	Surgery	Polar ligation 2 Stages	Normal Stillborn	Thyroidectomy 2 Stages post Dcl.	Subsequent pregnancy without difficulty
2	T. A.	2 Plus	Surgery	Thyroidectomy 1 Stage 6th Mo.	Live baby Normal	None	Excellent
3	T. A.	2 Plus	Surgery	Thyroidectomy 1 Stage 5th Mo.	Live baby Delivery, section	None	Excellent
4	T. A.	2 Plus	Admitted At term	None	Live baby Normal	Thyroidectomy 3 Mo. Postpartum	Death on table, P.M. Myocarditis. T.A.
5	T. A.	2 Plus	Conservative	None	1 Mo. premature Delivery, section	None	Excellent
6	T. A.	3 Plus	Conservative	None	Live baby Normal	Thyroidectomy 2 Stages 1 Mo. P.P.	Thyroid symptoms subsided
7	X. G.	3 Plus	Conservative	Pr. Thyroidectomy Polar ligation	1 Mo. premature Normal	None	Excellent
8	T. A.	3 Plus	Conservative With x-ray	2 Stages 8th Mo.	Live baby Normal	None	Died 15th post-partum day Pulmonary infarct
9	X. G.	2 Plus	Conservative	None	Live baby Normal	None	Symptoms subsided
10	X. G.	1 Plus	Conservative	None	Live baby Normal	Thyroidectomy 16 Mo. later	Excellent following operation
11	X. G.	2 Plus	Conservative With x-ray	Thyroidectomy 1 Mo. later	Live baby Normal	None	Excellent. B.M.R. -41 Subsequent pregnancy with- out difficulty
12	X. G.	1 Plus	Conservative	None	Live baby Normal	None	Improved
13	X. G.	2 Plus	Conservative	Pr. Thyroidectomy Thyroidectomy 3rd Mo.	Live baby Normal	None	Improved
14	X. G.	1 Plus	Surgery	None	Live baby Normal	None	Not followed
15	X. G.	1 Plus	Conservative	Thyroidectomy 4th Mo.	Live baby Normal	None	Excellent
16	X. G.	3 Plus	Surgery	None	Live baby Normal	None	Not followed
17	X. G.	1 Plus	Conservative	None	Live baby Normal	Thyroidectomy 2 Yr. later	Excellent
18	T. A.	1 Plus	Conservative	None	Live twins In hospital	Thyroidectomy to be done post- partum	—
19	T. A.	2 Plus	Conservative	None	At term		

cases of hyperthyroidism associated with pregnancy can be successfully carried through to normal delivery if properly managed.

Therapeutic abortion is favored by few authors today as a desirable method of relieving the hyperthyroidism. Fletcher has advised sterilization of all patients with hyperthyroidism whose delivery is accomplished by section but this advice may be open to question.

All authors are agreed that adenomatous goiter with hyperthyroidism complicating pregnancy is more serious than exophthalmic goiter but is fortunately less frequent. If the adenomatous goiter is accompanied by pressure symptoms or evidence of myocarditis, surgical therapy is definitely indicated. Four of our seven cases subjected to surgery during pregnancy were of this type and both of our maternal deaths were women with adenomatous goiter and hyperthyroidism. These patients seen near term must be very carefully supervised during their delivery and should have the benefit of thyroidectomy during the puerperium.

The use of iodine as a valuable therapeutic agent in the conservative treatment of hyperthyroidism during pregnancy is now generally accepted. There still exists some question as to its usefulness in adenomatous goiter with hyperthyroidism, but the former opinion that it definitely is contraindicated no longer holds. The value of Lugol's solution in controlling mild hyperthyroidism from exophthalmic goiter complicating pregnancy is now well established. These women tolerate small doses of iodine for prolonged periods during pregnancy, and in conjunction with rest and sedation the symptoms of hyperthyroidism may be adequately controlled until the pregnancy is terminated. Patients with exophthalmic goiter who do not respond to conservative measures may be safely subjected to thyroidectomy at any time this seems indicated. Those who are successfully carried through to the puerperium on conservative measures and who continue to evidence symptoms of hyperthyroidism should then be subjected to thyroidectomy.

Summary and Conclusions

1. A series of 19 cases of hyperthyroidism complicating pregnancy are reported.

2. The incidence of pregnancy in established thyroid disease is over three times as high as the incidence of hyperthyroidism developing during pregnancy.

3. The thyrotoxicosis was definitely aggravated by the pregnancy in 74 per cent of the series, increased in 21 per cent, and unaffected in 5 per cent.

4. Toxemia of pregnancy, varying in degree, occurred in 62.5 per cent of the eight patients admitted during the third trimester.

5. Eleven patients were treated conservatively and eight underwent surgery for their thyroid disease prior to delivery.

adenomatous goiter with mild hyperthyroidism. She was delivered of a live baby by section but died suddenly on the table. Post-mortem examination showed a large nodular goiter weighing 248 Gm. and a flabby, dilated heart with extensive evidence of myocarditis.

Discussion

The recorded experience of a group of authors with hyperthyroidism complicating pregnancy has been analyzed in Table VII. Of the total of 387 collected cases, 170, or 44 per cent, received surgical therapy for their hyperthyroidism prior to delivery and at least 7 patients required thyroidectomy following delivery. The remaining 217 cases (56 per cent) were treated conservatively. There were 7 recorded miscarriages and 4 therapeutic abortions. Eleven babies in the group died at delivery, an infant mortality of 2 per cent. There was only one recorded maternal death (0.26 per cent).

The opinions expressed in the literature regarding the correct method of managing hyperthyroidism complicating pregnancy have been somewhat divergent. In general there have been those who have favored conservatism in all cases, those who recommend thyroidectomy at any stage in the pregnancy, and a group who feel that every case must be individualized.

With the gradual accumulation of experience with thyrotoxicosis complicating pregnancy, and a better appreciation of the many factors requiring consideration, a definite trend toward individualization of the case is apparent. There can be little doubt that the pregnant woman with hyperthyroidism can successfully withstand a thyroidectomy, but the question remains the necessity and advisability of the procedure in all cases.

The combination of hyperthyroidism and toxemia of pregnancy in the same patient does not demand anything other than conservative therapy. The treatment of one condition in no way conflicts with the treatment of the other. Interruption of pregnancy should be considered only when it would be of definite value to the mother. The time of interruption will have to be individualized. The method used should be the one which will do the patient the least amount of harm and be most likely to result in ultimate recovery of the mother and in the production of a normal live child.

Falls, Hyman and Kessel, Luker, and others have pointed out the frequency with which the syndrome of exophthalmic goiter subsides during the puerperium with complete relief from symptoms. Falls states that one must accept a fetal mortality of 20 per cent from abortion, premature labor and other causes in cases subjected to thyroidectomy during pregnancy, but the collected figures do not appear to substantiate this statement. Hinton¹⁷ has advised interruption of the pregnancy in cases with adenomatous goiter associated with severe hyperthyroidism and myocarditis and in fulminating cases of exophthalmic goiter endangering the life of the mother. He concludes, however, that 90 per cent of the

ACTION OF MORPHINE IN OBSTETRIC ANALGESIA*

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THE present investigation represents an attempt to determine under conditions of laboratory control the action upon the fetus of morphine and its effect upon the mechanism of labor. Under clinical conditions the administration of morphine for the relief of pain during labor is attended by so many variable factors, especially those which are unforeseen, that the hazard of injury to the child or mother has remained obscure. Despite the considerable knowledge of the action of morphine which the pharmacologist has provided, the evidence from the obstetric standpoint is incomplete.

Furthermore, quantitative evaluation of the hazard of morphine during labor, not merely the recognition of the existence of such risk, is urgent in the measure that relief of pain is required. By analysis of the action of morphine, therefore, the aim is to work out a standard method of assay by which other drugs which are proposed for use in obstetrical analgesia may be compared with morphine.

Methods and Material

In the present experiments rabbits were selected for study. The response to morphine in this species is favorable for comparison with man. The animals were reared in the laboratory and were from selected stock which had been under supervision for many years. A standard diet of alfalfa, hay, oats, and cabbage was fed.

In order to eliminate the factor of the complications of labor, the effect of morphine upon the fetus was investigated by three methods. First, the effect on fetal respiratory movements was observed in animals prepared according to a technique previously described (Snyder and Rosenfeld, 1937) which permitted correlation of the effect on the maternal animals such as analgesia or respiratory depression, with that on the fetuses as seen through the wall of the unopened uterus. Second, the state of the fetuses was determined upon delivery by hysterotomy at various intervals varying from twelve minutes to fifteen hours after intravenous injection of the maternal animal. Third, following injection of the maternal animal the influence of morphine upon the resistance of the fetus to anoxia was measured in terms of the duration of respiratory movements when nitrogen was breathed instead of air, following delivery by hysterotomy. In addition, normal fetuses were

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6. One fetal death occurred, and there were two maternal deaths in this series.

7. Both maternal deaths occurred in patients with adenomatous goiter and hyperthyroidism, confirming the opinion that this is the most serious type of thyroid disease complicating pregnancy.

8. Thyroidectomy is a safe surgical procedure during pregnancy and should be undertaken at any stage if conservative treatment does not control the thyrotoxicosis.

9. The treatment of the patient with hyperthyroidism complicating pregnancy should be individualized. Surgical interference will be necessary more frequently in patients with adenomatous goiter and hyperthyroidism than in those with primary exophthalmic goiter.

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maternal animal was repeated three times at intervals of twenty minutes, and finally a dose of 10 times the initial one was given. Seven litters including 42 fetuses were observed. Depression of intrauterine respiratory movements may occur as the dose is increased and occasionally there is a transient interruption of rhythmical respiration. The outstanding result during observation of two hours or longer was the rhythmical breathing of the fetuses despite administration to the mother of 13 times the analgesic dose of morphine.

Furthermore, delivery of the fetuses by hysterotomy after several hours observation within the uterus was followed by rapid respiratory movements at birth. It was evident that marked depression of intrauterine respiration even involving a period of apnea as a result of narcosis did not necessarily produce irreversible damage of the respiratory system.

Effect of Morphine Upon the Fetus at Various Intervals After Injection.—In order to determine the effect upon the fetuses of a large dose of morphine (13 mg. per kg.) or about 13 times the dose required for an analgesic effect in the maternal animal, a series of sixteen animals was injected intravenously and the fetuses were delivered by hysterotomy at various intervals from twelve minutes to fifteen hours after administration of the drug. The litters were at term except in four animals which were delivered at a stage of prematurity. Hysterotomy was accomplished under novocain infiltration, thus avoiding a general anesthetic (Table I).

TABLE I. DELIVERY BY HYSTEROTOMY

RABBIT	STAGE OF PREGNANCY (DAYS)	DOSAGE OF MORPHINE I.V.		TIME ELAPSED FROM INJECTION UNTIL DELIVERY	FETUSES	
		MG./KG.	TOTAL MG.		ALIVE AND SURVIVED	DEAD
1	31	13	35	15 hr.	8	0
2	31	13	35	14 hr.	7	0
3	31	13	42	13 hr.	5	0
4	31	13	38	12½ hr.	5	1
5	31	13	39	1 hr.	5	0
6	32	13	41	40 min.	8	0
7	28	12	37	35 min.	9	0
8	29	13	35	35 min.	7	0
9	30	13	30	35 min.	5	0
10	30	13	41	30 min.	2	0
11	31	13	44	30 min.	1	0
12	31	13	44	30 min.	6	0
13	31	13	40	25 min.	4	0
14	32	13	31	20 min.	7	0
15	33	13	38	16 min.	4	0
16	32	13	32	12 min.	3	0

The outstanding result in a consecutive series of 86 fetuses was the survival of the entire group of fetuses following operative delivery. Only one fetus of the series was found dead within the uterus, and in this instance separation of the placenta with a large retroplacental hematoma was involved rather than fetal narcosis. The remaining five fetuses of this litter were alive and survived.

The fetuses at delivery showed marked differences in activity according to the interval which elapsed following administration of morphine.

injected directly with morphine and the time of survival in nitrogen was determined, using apparatus previously described (Rosenfeld and Snyder, 1938).

In order to determine the effect of morphine upon labor, the incidence of stillborn fetuses was observed following passage through the birth canal. The time of mating and ovulation were known accurately and morphine was injected exactly thirty-one days after mating. The length of pregnancy averaged thirty-two days in animals of this stock. One series of rabbits was injected at an earlier stage, namely, twenty-six days. Throughout pregnancy the animals were isolated in separate cages. Litters containing one or two fetuses were not included.

Morphine sulfate was used throughout, being injected into the ear vein during a period of one minute in a volume of 2 c.c. of distilled water. Dosage is expressed by weight of morphine sulfate and not of the alkaloid base.

According to Eddy, the minimal effective dose of morphine for respiratory effect in rabbits is 0.20 mg. per kg. morphine sulfate which is equivalent to 0.15 mg. per kg. alkaloid base; and for analgesic effect, using cats, the dose is 1 mg. per kg. morphine sulfate (0.75 mg. per kg. alkaloid base). Furthermore a striking inhibition of elimination of fecal contents from the alimentary tract was observed following dosage of 5 mg. per kg. morphine sulfate in rabbits and dogs. In our animals a definite analgesic effect was evident in the maternal animal following 1 mg. per kg. morphine sulfate.

In attempting to correlate the response to morphine in man and in the rabbit, it is of interest to note that the basal metabolic rate of the rabbit is 3 times greater than that of man, the oxygen consumption per kilogram per hour at rest being about 200 c.c. in man, in contrast to 650 c.c. in the rabbit (Krogh, 1940). Thus, a total dose of 16 mg. of morphine sulfate in a man of 70 kg. amounts to 0.23 mg. per kg., or if multiplied by 3, is three quarters of the dose used for analgesia in the rabbit.

The Effect of Morphine on the Fetus

Effect of Morphine Upon Fetal Respiration.—Changes in rate of intrauterine respiratory movements observed directly through the wall of the unopened rabbit uterus at full term afford a sensitive indicator for the detection of the earliest effect of narcosis in the fetus following administration of morphine to the maternal animal (Rosenfeld and Snyder, 1939). The degree and duration of respiratory depression permit evaluation in roughly quantitative terms of the extent to which a particular narcotic affects the fetus. Comparison by this method of morphine with other nonvolatile drugs, such as chloral hydrate, paraldehyde, and pentobarbital sodium revealed certain advantages of morphine.

In the light of these findings, observations were extended upon morphine as well as certain new derivatives of exceptional analgesic potency, available through the courtesy of the Committee on Drug Addiction, National Research Council (Snyder and Lim, 1941). With regard to morphine, it was found that respiratory movements of the fetuses were not abolished by a dosage which produced definite analgesia and respiratory depression in the maternal animal. Thus in a typical experiment a dose of 1 mg. per kg. of morphine sulfate intravenously in the

to survive after birth, even though delivery occurred at short intervals after injection when narcosis of the fetus was at a maximum.

The Effect of Morphine Upon the Resistance of the Fetus to Asphyxia.—Delivery by Hysterotomy After Administration of Morphine to the Maternal Animal: In view of the depression of respiratory movements and the sluggish motor responses following morphine, the question arose as to whether or not the defense of the fetuses against oxygen want was impaired by morphine narcosis. This point could readily be determined, since a base line of normal values was available, giving the time of survival in nitrogen of rabbits delivered at term or prematurely (Glass and Snyder, 1942). With the apparatus described previously (Rosenfeld and Snyder, 1938), kymograph records of the respiratory

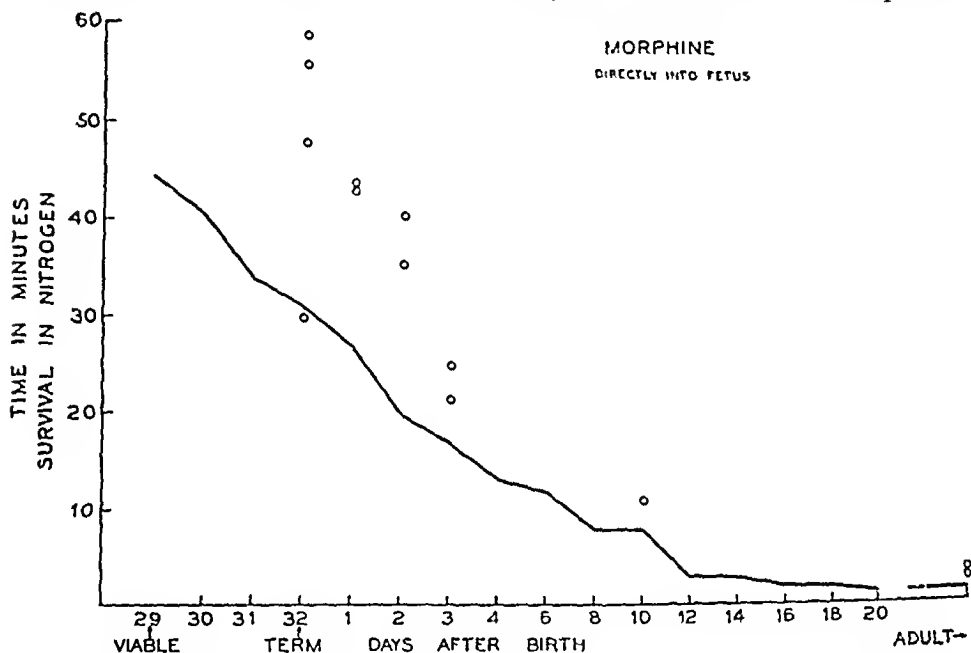


Fig. 2.—Effect of morphine on resistance of the fetus to anoxia. Morphine, 13 mg. per kg., was injected intravenously about one hour before breathing of nitrogen began.

excursions of fetuses which were breathing nitrogen instead of air were obtained by aid of a plethysmograph connected to a recording tambour. Following administration of morphine (13 mg. per kg.) intravenously to the maternal animal, the entire litter of fetuses were delivered by hysterotomy (after local novocain infiltration) at intervals of twelve to forty minutes after injection. Observations were made successively on about three fetuses of a litter. Results were based upon twenty-four fetuses from nine litters delivered at twenty-nine to thirty-two days (Fig. 1).

Observations showed that after morphine, there was no decrease in the time of survival of fetuses when breathing nitrogen instead of air. Contrary to common belief, it was found that respiration continued for a longer time in the fetuses which were under the influence of morphine than in those in the series of normal controls.

Furthermore, these findings were supported by observations on the remaining fetuses of the litter one or two days after delivery, when narcosis was no longer evident. In six fetuses obtained from three

In litters at term which were delivered less than one-half hour following intravenous injection of the maternal animal, the fetuses showed marked signs of narcosis, body movements were sluggish, response to stimulation was retarded, and respiratory activity was depressed. In the fetuses delivered at a later time within the first hour after injection no further increase in degree of narcosis was noted. It is interesting to note that among this group were included twenty-three fetuses delivered at a stage of prematurity. In the litters delivered twelve to fifteen hours after morphine, the fetuses crawled about and attempted to suckle, their activity being indistinguishable from that of untreated controls.

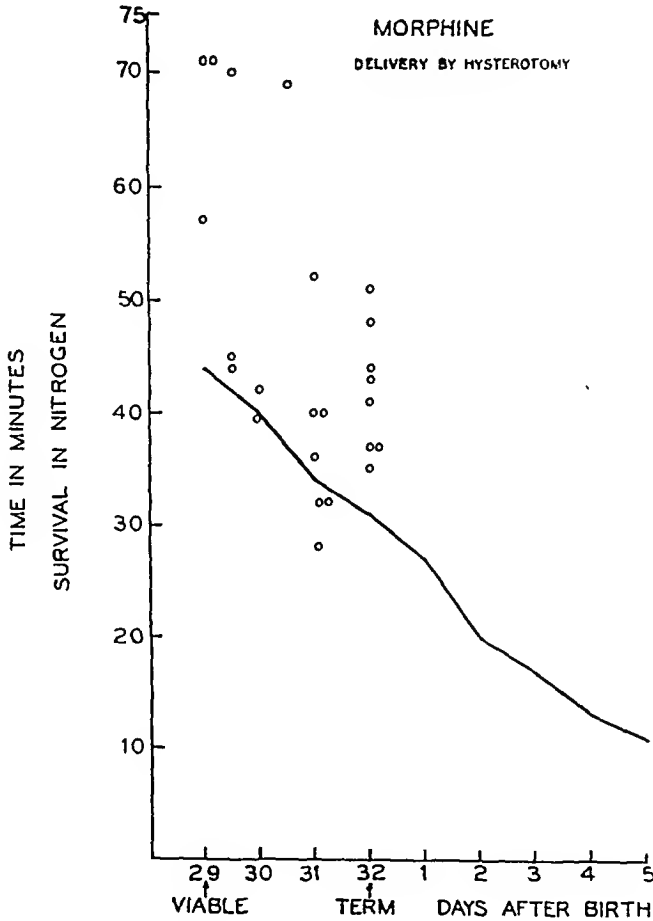


Fig. 1.—Effect of morphine on resistance of the fetus to anoxia. Circles show duration of respiratory movements of fetuses in nitrogen, the survival time being prolonged rather than shortened. The base line is the average survival time in a series of 200 normal fetuses. The maternal animal received morphine, 13 mg. per kg., intravenously about one-half hour before hysterotomy.

In the foregoing series of animals delivery by hysterotomy eliminated the factor of labor and thus permitted evaluation of the effect of narcosis of the fetus following morphine entirely independent of the complications which attend delivery through the birth canal. It is of particular significance from this standpoint that administration of large doses of morphine sufficient to cause deep analgesia of the maternal animal did not result in intrauterine death of the fetuses or in failure

of a series but rather are grouped chiefly in certain litters. In this connection it is interesting to consider the frequency with which labor is attended by the expulsion of at least three dead fetuses in a litter, a number which is definitely in excess of the average incidence (Table III).

TABLE III. SPONTANEOUS BIRTH

MOR- PHINE MG./KG.	STAGE OF PREGNANCY AT INJECTION (DAYS)	LITTERS			STILLBORN FETUSES				PROLONGED LABOR	
		TOTAL.	WITH EXCESSIVE STILLBIRTHS		TOTAL		PORTION IN LITTERS WITH EXCESSIVE STILLBIRTHS			
			NO.	%			NO.	%	NO.	%
None	--	41	5	12	32	12	24	75	4	10
13	31	32	19	59	124	57	111	89	13	41
13	26	20	2	10	17	12	12	71	0	0
1	31	44	9	20	63	23	49	78	7	16

First, in the series of control animals in which morphine was not injected, in the course of spontaneous delivery of 41 litters there were five litters, or 12 per cent, which had three or more stillborn fetuses. Second, in animals in which a large dose of morphine (13 mg. per kg.) was given at thirty-one days in the birth of 32 litters, there were 19 litters, or 59 per cent, in which at least three fetuses were dead at birth. Third, in the series of 20 litters in which 13 mg. per kg. of morphine was injected at twenty-six days, there were only two litters, or 10 per cent, which had at least three stillborn fetuses. Fourth, in animals in which a small dose of morphine (1 mg. per kg.) was given about the time of labor (thirty-one days), in a series of 44 litters there were nine litters, or 20 per cent, which had three or more stillborn fetuses. It was evident that the frequency of the occurrence of labor which was so altered as to result in three or more stillborn fetuses in a litter corresponded closely to the frequency of occurrence of stillborn fetuses. Thus, in the four groups of animals cited above, labor was marked by excessive stillbirths in 12 per cent, 59 per cent, 10 per cent, and 20 per cent of the litters, respectively, while the fetal mortality of the corresponding groups was 12 per cent, 57 per cent, 12 per cent, and 23 per cent.

Furthermore it was interesting to note how many of the stillborn fetuses were found in litters having excessive stillbirths. Thus, in the control series of 260 fetuses, there were 32 stillborn, or 12 per cent; of these 32 dead fetuses, 24, or 75 per cent, belonged to litters which had at least three stillborn. In the series of 217 fetuses born after injection of 13 mg. per kg. of morphine at thirty-one days, there were 124 dead, or 57 per cent; of these 124 stillborn, 111, or 89 per cent, occurred in litters which had three or more stillborn. In the series of 138 fetuses born after the injection of 13 mg. per kg. of morphine at twenty-six days, there were 17 stillborn or 12 per cent; of these 17 dead fetuses, 12, or 71 per cent, were in litters which had at least three stillborn. Finally, in the series of 275 fetuses born after a dose of 1 mg. per kg. of morphine at thirty-one days, there were 63 stillborn, or 23 per cent; of these 63 dead fetuses, 49, or 78 per cent, were in litters which had three or more stillborn fetuses.

litters twenty-one hours or more after delivery, the time of survival in nitrogen was markedly shortened in contrast to that observed during narcosis.

Direct Injection of Morphine Into the Fetus.—The effect of morphine upon the tolerance to anoxia was further tested by direct injection of morphine (13 mg. per kg.) intravenously in the newborn rabbit. The animals were exposed to nitrogen within an hour following injection and respiratory tracings were obtained as previously described. Observations on thirteen animals in which nitrogen was breathed instead of air revealed no decrease in time of survival after direct injection of morphine. In fact, respiration continued for a longer time in this group than in normal controls (Fig. 2).

The Effect of Morphine on Labor

Striking evidence of the effect of morphine on the labor mechanism is afforded by increased incidence of stillbirths when the fetuses are expelled through the birth canal in contrast to delivery by hysterotomy. Following the injection of a large dose of morphine (13 mg. per kg.) at thirty-one days which is about the time of the onset of labor, spontaneous parturition involving a total number of 217 fetuses resulted in the birth of 93 living and 124 dead ones, or a fetal mortality of 57 per cent. In contrast, in a control series of 260 births occurring spontaneously in which morphine was not injected, there were 228 living and only 32 stillborn, or a fetal mortality of 12 per cent (Table II).

TABLE II. SPONTANEOUS BIRTH

MORPHINE DOSAGE MG./KG.	STAGE OF PREGNANCY AT INJECTION (DAYS)	STATE OF FETUSES AT BIRTH		FETAL MORTALITY (PER CENT)	TOTAL NUMBER OF FETUSES
		ALIVE	DEAD		
None	--	228	32	12	260
13	31	93	124	57	217
13	26	121	17	12	138
1	31	212	63	23	275

Furthermore, the administration of morphine at an earlier stage of pregnancy, i.e., twenty-six days, was followed by no marked increase in stillbirths such as occurred after injection at the time of labor. In animals injected at twenty-six days with 13 mg. per kg. of morphine, in a series of 138 births, there were 121 living and 17 dead fetuses, or a fetal mortality of 12 per cent.

There was evidence that increase in stillbirths followed the administration at the time of labor of even a small dose of morphine, i.e., 1 mg. per kg., or approximately the amount which is required to elicit analgesia. Following injection of 1 mg. per kg., of morphine at thirty-one days, in a total series of 275 births, there were 212 living and 63 dead fetuses, or a fetal mortality of 23 per cent.

Analysis of the distribution of stillbirths among various litters of the series throws light upon the manner in which morphine influences the labor mechanism. Stillbirths do not occur uniformly among the litters

pregnancies terminated with excessive stillbirths instead of 12 per cent. Examination of the dead fetuses showed that they had been alive before parturition. In this group of 59 per cent of the animals, there occurred 89 per cent of the stillbirths. It was evident that following morphine the increased number of stillborn fetuses were not uniformly distributed among all of the injected animals but, on the contrary, stillbirths were grouped chiefly in certain animals.

It is interesting to note the effect upon the functional efficiency of the labor mechanisms of morphine in dosage of 1 mg. per kg. which results in definite analgesia in rabbits and is within the range of dosage employed therapeutically. Pregnancy terminated with excessive stillbirths about twice as frequently as in uninjected controls, and the fetal mortality likewise was doubled in this series.

Additional evidence that the increased incidence of fetal mortality was not a direct effect of the action of morphine upon the fetus but rather resulted from injury of the mechanism of labor was obtained by direct observation of fetuses under conditions which eliminated the complications of labor, while keeping constant the dosage level of morphine. For example, following a large dose of morphine the fetuses were alive and survived when delivered by hysterotomy instead of by extrusion through the birth canal. Similarly, the persistence of fetal respiratory movements following injection was observed directly through the wall of the unopened uterus. Direct injection of fetuses with morphine 13 mg. per kg. following delivery did not result in death. In fact, in experiments in which the resistance to asphyxia was tested by the breathing of nitrogen instead of air, the time of survival of the fetuses injected with morphine was not less than that of normal controls.

From the pharmacologic standpoint the present experiments illustrate methods for the laboratory assay of drugs proposed for use in obstetric analgesia. As applied in the case of morphine, two findings especially stand out. First, the action of morphine on the labor mechanism as revealed by increase in fetal mortality brings to light a striking effect on the maternal organism. Second, in the case of the effect of morphine upon the fetus, especially noteworthy is the evidence of the resistance of the fetus to asphyxia under conditions of the experiments despite large dosage of morphine.

Clinically, so far as the findings in the rabbit have a bearing, it is evident that the functional efficiency of the labor mechanism is of prime interest in the problem of obstetric analgesia. Since the question as to whether or not the labor mechanism is normal ultimately depends upon direct observation during labor, it is clear that familiarity with pharmacologic findings regarding the average analgesic dose of the drug may not reveal fully the hazards of use during labor. Knowledge of the course of labor is of first importance in the practice of obstetric analgesia.

Marked prolongation of labor increased in frequency following the administration of morphine at the time of labor. Usually a litter of rabbits is born in less than an hour, while after injection of morphine at thirty-one days, expulsion of fetuses during a period of six to thirty-six hours was not uncommon. Thus following 13 mg. per kg. of morphine at thirty-one days, in a series of 23 litters, marked prolongation of labor was noted in 13 litters, or 41 per cent. In contrast, in a control series of 41 litters in which morphine was not injected, prolongation of labor was observed in four litters, or only 10 per cent. After 1 mg. per kg. of morphine or approximately the analgesic dose, injected at thirty-one days in a series of 44 litters, prolonged labor was seen in 7 litters, or 16 per cent. No increase in incidence of prolonged labor was noted, however, when large doses of morphine (13 mg. per kg.) were given about a week before term, e.g., at twenty-six days.

Discussion

From the foregoing findings it was evident that following the injection of morphine in large dosage there was a striking increase in fetal mortality and in the incidence of prolonged labor, when the drug was administered at the time of the onset of labor. In contrast, when the same amount of morphine was given five days before the onset of labor, no such effect was noted.

In explanation of the influence of morphine upon the emptying of the uterus it is interesting to bear in mind the striking effect of this drug upon the emptying of the alimentary canal. Evacuation of the contents of the bowel was delayed twenty-four hours in dogs following morphine in dosage of 6 mg. per kg. (Kreuger, 1937). In rabbits, Eddy (1932) found that the minimal effective dose for suppression of gastrointestinal evacuation was 6 mg. per kg. of morphine. Furthermore, there was evidence that the suppression obtained with morphine was a specific effect upon gastrointestinal activity rather than the result of general depression induced by the narcotic, since the administration of definitely depressant doses of various hypnotics failed to suppress intestinal evacuation, for example, di-ethyl barbituric acid 100 mg. per kg., or chloral hydrate 150 mg. per kg. In the human being, the medicinal use of opium for the alleviation of diarrhea has been recognized for centuries.

How frequently the labor mechanism fails to function at a level of activity adequate for the birth of living offspring was revealed in the series of uninjected animals, in which 12 per cent of the pregnancies terminated with excessive stillbirths. In this group of 12 per cent of the animals, there occurred 75 per cent of the stillbirths. There was evidence that death occurred at the time of parturition since the fetuses were of full-term development, rarely macerated, and at autopsy no gross defects were noted upon macroscopic examination.

After the administration of morphine 13 mg. per kg., about the time of onset of labor, there was evidence of an increase in the functional failure of the birth mechanism to the extent that 59 per cent of the

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THE NATURE AND SIGNIFICANCE OF THE GROOVED NUCLEI OF BRENNER TUMORS AND WALTHARD CELL ISLANDS

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THE nuclei of the epithelial cells found in a Brenner tumor show a characteristic longitudinal grooving or folding that makes them resemble the kernels of the breakfast cereal known as "Puffed Wheat" (Fig. 1). This appearance is conspicuous when the ordinary high power of the compound microscope is employed.* It is strange that the numerous descriptions published in the last ten years concerning this tumor have mostly ignored this strikingly obvious feature. One might assume that "study" of the tumor has in most cases been restricted to low-power inspection.

Varangot (1938) was apparently the first to mention specifically the frequent occurrence of what he interpreted to be "*une sorte de bâtonnet allongé suivant le grand axe du noyau et le divisant en deux parties.*" But before the time of his publication, and since, this "rod" has appeared in photomicrographs illustrating the tumor (e.g., Meyer, 1932; Plaut, 1933; Gnassi, 1937; Timmerberg, 1939; Hicks, 1941; Grayzel and Friedman, 1941). Recently Danforth (1942a), unaware of Varangot's publication,† has described this feature as a new discovery and has furnished excellent photographs and drawings to illustrate its appearance in both Brenner tumors and Walthard cell islands. Previously, in a communication to me, Dr. Danforth had independently made the same interpretation of this marking as did Varangot, by referring to the nucleus as showing a "line" or "rod." In reply, I pointed out that this was not the case. On the contrary, the appearance was more like a plate, whereas careful study indicated that the effect was produced by folding, although in many instances the adjoining surfaces were closely approx-

*In experiments with controlled staining the marking was found to be visible regardless of the intensity of the stain. It was even plainly discernible in unstained sections. These results do not agree with Danforth's (1942a) conclusion as to visibility only under optimum conditions.

†While Danforth's article was in press I informed him of the existence and nature of Varangot's contribution and he has since acknowledged Varangot's priority in a letter to this JOURNAL (1942b).

Summary

1. Increased incidence of stillbirths following the administration of morphine during labor in rabbits is due to the effect upon the mechanism of labor chiefly, rather than to a direct effect upon the fetus.

2. Fetal mortality in the birth of 890 fetuses obtained from 137 litters was as follows: (1) normal controls, 12 per cent; (2) after morphine 13 mg. per kg. at thirty-one days, i.e., the onset of labor, 57 per cent; after morphine 13 mg. per kg. at twenty-six days, i.e., before the onset of labor, 12 per cent; after morphine 1 mg. per kg., i.e., an analgesic dose, at thirty-one days, 23 per cent.

3. Stillbirths were not uniformly distributed but involved chiefly certain litters as follows: (1) normal controls 12 per cent of the litters; (2) after morphine, 13 mg. per kg., at thirty-one days, 59 per cent; after morphine, 13 mg. per kg., at twenty-six days, 10 per cent; after morphine, 1 mg. per kg., at thirty-one days, 20 per cent of the litters.

Similarly, marked prolongation of labor was noted in certain litters, the incidence being, respectively: (1) 10 per cent, (2) 41 per cent, (3) none, and (4) 16 per cent.

4. Prior to the onset of labor, the fetuses were alive and survived despite administration of morphine to the maternal animal in large dosage (13 mg. per kg.), as shown in the following experiments:

a. By direct observation of intrauterine respiratory movements during a period of two hours or longer, it was found that rhythmical breathing of the fetuses was depressed but not abolished.

b. By hysterotomy, in contrast to expulsion through the birth canal, fetuses were regularly delivered alive at intervals of twelve minutes to fifteen hours following injection.

c. By measurement of the time of survival of fetuses when breathing nitrogen instead of air, it was found that following morphine the resistance to anoxia was not decreased.

5. In considering the clinical use of morphine in obstetric analgesia, it is of interest to note that under controlled experimental conditions morphine definitely increased fetal mortality by injury of the mechanism of labor and, following a dosage within the range employed therapeutically, the frequency of labor with unfavorable outcome was doubled. Since prognosis regarding the functional efficiency of the labor mechanism depends upon direct observation during labor, it is clear that there is reason to limit administration of morphine until evidence of normal function is obtained.

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The marking usually does not extend the full length of the nucleus (*a, b, c*) and may be curved (*a, j*). At one pole the nucleus is frequently bifid, the converging margins of the notch continuing as the median, longitudinal plate (*b, c, g, k, n*). But both ends may be involved, in which case the appearance is somewhat like that of a complete coffee bean (*f, l*).

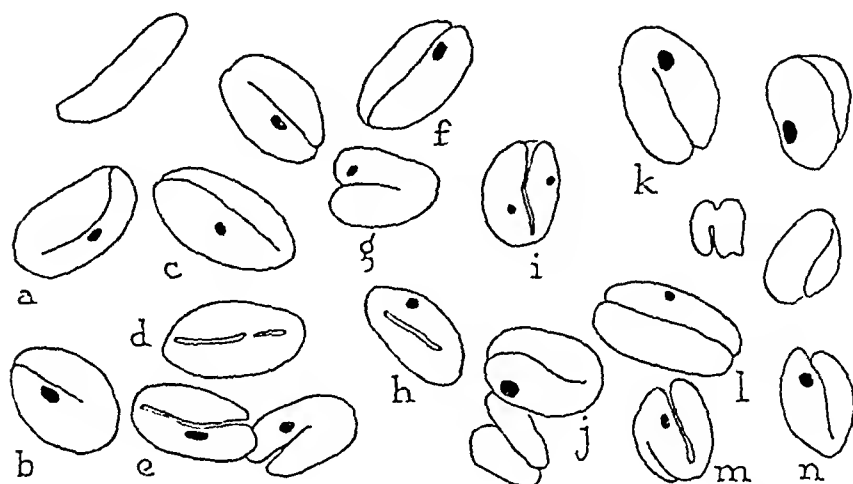


Fig. 1.—The nuclei of a Brenner tumor, as they occurred in a small area of a section. Cell outlines and chromatin masses have been omitted. Camera lucida drawings; $\times 1500$.

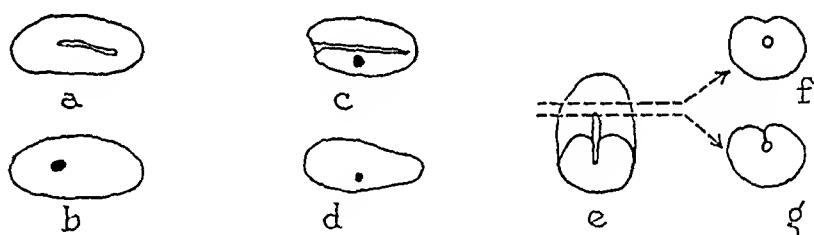


Fig. 2.—Changing appearances of Brenner nuclei, due to focusing. A high and low focus on the same nucleus is shown in *a* and *b*. A similar change produced by focusing is illustrated in *c* and *d*. Three different appearances of the same nucleus, transversely sectioned, are shown in *e, f*, and *g*; to section *e*, half of the nucleus has been added and broken lines indicate the levels of sections *f* and *g*. Camera lucida drawings; $\times 1500$.



Fig. 3.—Transverse sections of Brenner nuclei, showing grooves and "plates." Camera lucida drawings; $\times 1500$.

In direct view, the line- or platelike appearance can be resolved under favorable conditions into a double line (Fig. 1, *e, h, i*). This may be of longer or shorter extent and at times two grooves can be seen in line, but separated (*d*). The parallel lines are really the margins of a local groove or fold, as focusing proves (Fig. 2, *a, b* and *c, d*). This groove extends into the nucleus to varying depths (Figs. 3, *a* and 5, *a, d*). Its longitudinal excursion may include the whole length of the nucleus; the

imated. In his publication Dr. Danfórh has characterized the nucleus as exhibiting a groove or fold.

The presence of this structural peculiarity in the nucleus of the cells of Brenner tumors and Walthard islands is sufficiently well established and is easily verifiable. The frequency of occurrence is variable. In many specimens of Brenner tumors these deformed nuclei are so abundant that almost every nucleus seen is an example (Fig. 1); in other samples they are sparse. In some tumors they are common in certain regions and rare in others. It seems highly improbable from the 11 specimens I have examined that Varangot's generalization (from the study of three specimens) that such nuclei are more numerous at the extreme periphery of the cell cords would stand the test of statistical enumeration.

Rather than to dwell further on these general matters it is my purpose to present some detailed information on the nature of this type of nuclear deformation and on its occurrence and possible significance in these tumors and elsewhere. Many authors have described the Brenner tumor cells as being arranged in a pavement epithelium, but this is obviously incorrect with respect to any ordinary meaning of this term. Since the cells are grouped in cords and masses, they are polyhedral in shape, and when not influenced by some modifying influence they are isodiametric. Lewis (1933) has proved that epithelial cells, subject only to equalized mutual pressures, tend to assume a 14-surfaced shape that in section appears most commonly as a six-sided figure. Such a section naturally resembles a flat, pavement epithelium in surface view. At the extreme periphery of a cord, the outermost cells frequently do assume the nature of a somewhat flattened basal layer. The granular cytoplasm is reticular to alveolar in texture and stains lightly in a neutrophilic manner. Cell boundaries are often indistinct to the point of becoming lost in a syncytium. A shrinkage space rather characteristically surrounds the nucleus. The ovoid nucleus is not small, as sometimes described, but measures up to 6 by 10 μ . The notion of smallness, perhaps, comes from cross sections, and especially from the divided appearance in some of these (Fig. 5, *c, e, g*). The nucleus contains many small chromatin masses, and usually a single, prominent, rounded nucleus. Varangot (1938) is wrong in his assertion of the general occurrence of several nucleoli, although two nucleoli are not uncommon (Fig. 1, *i*). He has presumably included karyosomes among his "nucleoli."

The distinctive alteration of the nucleus, already mentioned, is the result of grooving or infolding. The details of this phenomenon are best seen by the use of an apochromatic oil immersion lens with compensating oculars in a binocular microscope, but such equipment is not wholly necessary. When a nucleus is viewed lengthwise and at a slight slant, the appearance is that of a single line or plate. On focusing, this may prove to be one margin overriding another surface (Fig. 1, *c, f, g, j, n*).

shown in their Fig. 443. On the other hand, Stieve (1930), in his authoritative work on the male genital system, is misleading in his statement concerning these nuclei: "Gewöhnlich ist die Oberfläche der Kernes ganz glatt, zeigt keinerlei Rauhigkeiten, Höcker oder Einbuchtungen." Much the same type of infolded nucleus characterizes the cells of the rete testis, as van Ebnér (1902) and Stieve (1930) correctly specify. I have also observed it plentifully in the epithelium of the uterine tube, cervical glands of the uterine and seminal vesicle. Champy and Carleton (1921) claim that furrowed or canalized nuclei are more common than is generally supposed (*cf.* also Guieysse-Pellissier, 1926) and have described occurrences in human and comparative material, including the epidermis, cartilage, sex cells, interstitial cells of the testis, Wolffian duct, nerve cells, enteric epithelium, and lymphocytes. That these authors interpreted some of these examples as localized infoldings (canaliculi) is of no importance. Somewhat similar nuclear appearances have been described for the salivary glands (Garnier, 1900; Guieysse-Pellissier, 1926); gastric glands (Cade, 1901) and epididymis (Henry, 1900). Doubtless many other citations exist in the literature.

The proper explanation of this specialized nuclear configuration is not easy. Five possible explanations at once come to mind: (1) pressure deformation; (2) amitotic activity; (3) nuclear regression; (4) genetic relationship; and (5) surface increase for functional reasons.

1. Pressure Deformation.—Champy and Carleton (1921) have argued with some force that nuclear shape is often due to pressure exerted by various cell inclusions such as fat, yolk, or tonofibrils. The nuclei of cardiac muscle show a pleating of the nuclear membrane, each incision corresponding to a Krause's (Z) membrane. Variations in surface tension at the interfaces of nucleus and cytoplasm may be responsible for nuclei of irregular shape, but this is difficult of proof.

It is true that the cells of a Brenner tumor are crowded and, as they increase, are subject to restraint by the metamorphosis of adjacent ovarian stroma into a fibrous (collagenous) investment. But the cytoplasm is both abundant about these nuclei and is seemingly free from inclusions that might act in the manner Champy and Carleton specify. It is by no means clear how a generalized pressure could result mechanically in longitudinal folding of the Brenner nuclei.

The Sertoli cells are also crowded and their cell bodies are deformed by proliferating sex cells, and especially by the enlarging primary spermatocytes that lie at the level of Sertoli nuclei. In this instance the pressure is specifically against the lateral surfaces of the columnar Sertoli cells, but the nuclei themselves are not directly affected, and again the mechanics of nuclear deformation present difficulties of explanation. Moreover, I have found that the same nuclear shape is seen in the Sertoli cells of cryptorchid testes and in the atrophic seminiferous tubules of old age; in both instances this type of cell is about the only kind seen, and there is no crowding. Neither can generalized pressure explain satisfactorily the abundant occurrence of folded nuclei in the rete testis and many other locations. The suggestion of Champy and Carleton (1921), that nuclear folds or canaliculi may be produced by a mutual cell pressure that inhibits expansion of the nuclear membrane, is not very convincing.

extent may pass from one end part way toward the other (Fig. 2, *c*); or it may be without relation to either end (*a*). The ends of the groove may extend tunnel-like for a short distance into the interior of the nucleus (Fig. 2, *e-g*). This is a type of canalization. In my experience, indentations of the nuclear membrane are even more plainly seen as double lines in the Sertoli nuclei than in Brenner tumors.

The next question is whether all the markings are caused by grooves, or whether some of them correspond to superficial lines (linear thickenings of the nuclear membrane) and solid plates grown inward from such local thickenings, as Regaud (1900; 1901) believed to be the case in Sertoli nuclei. It is my belief that the fundamental process is grooving or folding. The evidence, best obtained from transverse sections, for this conclusion is as follows: (1) Shallow notches are commonly seen (Fig. 3, *a*), but no local thickenings of the nuclear membrane have been observed and no solid plates as short as the shortest notches; (2) grooves are far more evident than in random surface views of the nuclei; (3) grooves are more common than plates; (4) a "plate" tends to be thicker than the ordinary nuclear wall (Fig. 3, *b, c*); and (5) the plate may separate along its deep border and become a tube, or even a double tube (Fig. 3, *d, e*). If solid plates grow in from the nuclear membrane, one would expect to find early stages of them, but these are lacking. A plate would not necessarily have to be twice as thick as the nuclear membrane, but if a "plate" is produced by the approximation of the two walls of a fold, then the combined walls would have the thickness observed. A surface notch that continues inward as a plate can be interpreted as a plate undergoing splitting (Fig. 3, *b, c*), but it can also be interpreted as a region with both separate and apposed walls of a fold (Figs. 3, *b, c* and 5, *a, d*). The reason why shallow grooves do not have their walls in apposition is possibly due to the mechanical stiffness of the nuclear membrane (Fig. 4, *a*); a similar tendency for the groove to remain open is exhibited at its fundus (Fig. 3, *a*). Macklin (1916), studying living cells grown in tissue culture continuously for long periods, likewise concluded that apparent partitions extending inward from the nuclear wall are really reduplications of the nuclear membrane, the apposed surfaces being in close contact.

The next point of inquiry concerns the specificity of this type of longitudinal grooving. Although it is common and characteristic of the Brenner tumor and Walthard island, such grooving is not specific to these entities. It can be found also occasionally in the nuclei of connective tissue, smooth muscle, and ordinary epithelium. The fact that the nuclei of the ovarian stromal cells show occasional typical examples gives no convincing support to a stromal origin of these tumors, because the same appearance can also be seen at times in an hypertrophied, euboidal germinal epithelium of the ovary.

"Wrinkling," with folds extending deep into the interior, is frequently observable in the nuclei of the Sertoli cells of the testis, as has been known from the time of Benda (1887; 1898) and von Bardeleben (1892; 1897); Regaud (1900; 1901) has described this condition fully for the rat. Among textbooks, Maximow and Bloom (1942) state the situation correctly for Sertoli nuclei and illustrate it in 17 out of the 49 nuclei

was attained. The Brenner tumor is admittedly very slow growing. In view of the infrequency with which mitoses are seen in many faster growing tissues, one should not argue too strongly that amitosis must be the method by which these tumor cells proliferate. Even admitting that amitosis does occur in animal cells, and that it conceivably may be found in a Brenner tumor, it is certain, nevertheless, that amitosis alone cannot explain the prevalence of folded nuclei in this tissue.

3. *Nuclear Regression*.—Niessing (1888), Tellyesniezky (1897) and La Vallette St. George (1898) have interpreted the folded state of the Sertoli nuclei as stigmas of degeneration, and Stieve (1930) has suggested the same for the nuclei of the rete testis. On the contrary, Benda (1898) and Regaud (1901) do not agree with such an interpretation. If this explanation were correct, one might expect to see similar occurrences in the frankly regressive nuclei of the involuting corpus luteum and in such senescent cells as those of the zona reticularis of the suprarenal gland. Assuming the adequacy of such an explanation, one might then speculate on whether or not the regional variability in the occurrence of folded nuclei in Brenner tumors is indicative of differences in age or functional experience among the cell cords. On the other hand, a regression theory for the Brenner nuclei is seemingly contrary to what can be observed. These cells give no appearance of general retrogression or obsolescence.

4. *Genetic Relationship*.—It is theoretically possible that the cells of Brenner tumors and Walthard islands are ectopic representatives of cells normally located elsewhere. The similar longitudinal marking of the nuclei of the Sertoli and Brenner cells has impressed Danforth (1942a) who, seemingly unaware of the existence of other examples of this modified nuclear form, alludes guardedly to a possible relationship "which may solve the riddle of the histogenesis of the Walthard rest, the Brenner tumor," etc. Although such a genetic relationship between the Sertoli and Brenner cells may seem to many to be much too speculative to merit serious consideration, yet if any ectopic cell with this nuclear shape is to become suspect, probably the Sertoli cell qualifies best.

The inclusion within the ovary and its adnexa of nongerminal, male-line gonadal cells that later differentiate into specific tumors is, nevertheless, not so simple an hypothesis as at first appears. Numerous perplexing questions arise concerning the prospective potencies of the primitive gonad, its bisexuality, the single (indifferent) or dual (male-female) representation of supporting cells for the gonad, the homology of Sertoli and follicle cells, and the uniqueness of the secondary, definitive ovarian cortex. But some logical difficulties arise even if the possibility of the inclusion of Sertoli-like cells within the ovary and their subsequent differentiation into Brenner tumor cells be assumed. Why, for instance, does an ovarian location (and influence?) lead to a higher frequency of grooving among these cells and a lack of grooving in the rete ovarii cells, when in the male the Sertoli nuclei show less frequent grooving along with abundant, altered nuclei in the cells of the rete testis? In this regard there is no question but that the same primordium becomes either rete testis or rete ovarii, depending upon the swing of sex. The absence of grooving in the nuclei of the rete ovarii (Danforth, 1942a) is astonishing under this hypothesis, since the rete and Sertoli cells in the testis are merely different manifestations of the same basic, nongerminal cell of the gonadal primordium.

2. *Amitosis*.—Folded or indented nuclei have long been accepted by some observers as stages illustrative of amitotic nuclear division. This conclusion is largely circumstantial, and, as a generalization, has been viewed with considerable scepticism by many authorities. Lambert (1913) and Lewis and Lewis (1924) have never succeeded in following a single instance of direct cleavage in the nuclei of living cells in tissue culture. In living cells many nuclear constrictions proceed toward apparent completion and then the nucleus returns to its original shape (Macklin; 1916; Lewis and Lewis, 1924).

It has been claimed that mitoses are extremely rare, if not lacking, in cells whose nuclei are incised or canalized (Champy and Carleton, 1921). This would leave amitosis as the only method of cell division open to such cells and invites an interpretation of nuclear incisions as stages in amitosis. Since mitosis has never been reported in a Brenner tumor, an interpretation of amitosis for these atypical nuclei has some theoretical attractiveness despite the unorthodox longitudinal direction of the folding and the occurrence at times of more than one fold (Figs. 1, m and 4). Varangot (1938) has subscribed fully to an amitotic ex-

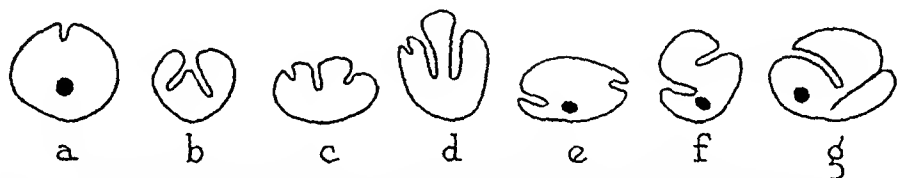


Fig. 4.—Transverse sections of Brenner nuclei, illustrating simple, branched, and double or triple grooves. Camera lucida drawings; $\times 1500$.

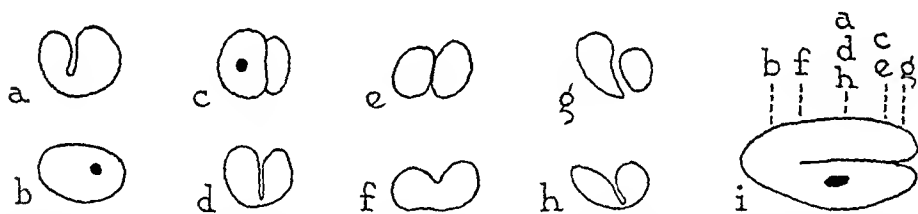


Fig. 5.—Transverse sections of Brenner nuclei. *a*, *c*, *e*, and *g*. Focal levels that might be thought to illustrate stages of amitosis. *b*, *d*, *f*, and *h*. Deeper focal levels of the same sections that modify the previous judgment. *i*. A nucleus, with the levels of sections *a*-*h* suggested. Camera lucida drawings; $\times 1500$.

planation for the Brenner tumor nuclei. Regaud (1900), like Bardeleben (1897) and others, originally considered the folded Sertoli nuclei to be undergoing amitosis, but later (1901) he rejected this interpretation, as have Maximow and Bloom (1942). In view of the prevalence of folded nuclei in a Brenner tumor, if amitosis is common there should be adequate and abundant evidence of completely partitioned nuclei and of separate nuclei lying side-by-side within a single cell body. On the contrary, such evidence is lacking. To be sure, instances of cross-sectioned nuclei can be found with two separate or apposed parts. But very many more sections can be found that show discrete nuclear moieties at one focus and joined parts at another focus (Fig. 5, *c*-*h*). Nuclei are frequently bifid (Fig. 5, *i*), and hence single cross sections that happen to show two nuclear moieties are valueless as critical evidence favoring a binucleate state. It is necessary to insist again, as many have done before, that the mere presence of two nuclei within a single cell body offers no proof of the method by which the binucleate state

rat, the comparison of the extremes of activity and inactivity among Sertoli nuclei would be still more striking.

Passing to the Brenner tumor nuclei, it is possible that the most satisfactory explanation of their modified form (Fig. 4) may be found in one or the other of the conditions just discussed. Of the two, vigorous metabolism has far more support by collateral evidence. If it be objected that definite proof of marked functional activity is lacking, several rejoinders are possible. Present ignorance of the functional role of this relatively new tumor type does not necessarily imply actual functional impotence. Moreover, Marwil and Beaver (1942) have recently described a case (and reviewed some allied instances) in which a Brenner tumor was associated with postmenopausal, uterine bleeding, and other changes usually associated with the presence of estrogens. They have suggested that the tumor might be responsible for the output of ovarian hormone. In this regard one may point out that if the origin of the Brenner tumor should prove to be from the ovarian epithelium, as my critical case seems to indicate, then such an endocrine activity is wholly consistent. The modern trend is to attribute the origin of functional ova and follicles to postpubertal oogenesis from the germinal epithelium (Evans and Swezy, 1931; Everett, 1943). The follicular epithelium is also suspect as the producer of the follicular hormone.

But it would be unwise at present to urge too strongly that the folded nuclear membrane of the Brenner tumor nucleus is correlated with accelerated cellular activity. Too little is known of the general applicability of such an interpretation, since this nuclear form is represented in all the fundamental tissue groups (but only in certain examples of each). In some gland and nurse cells the correlation between nuclear shape and high functional activity is good. In certain other instances of presumably high functional activity, the correlation fails. And in some instances the presence of this nuclear type is both unexpected and puzzling to explain on the basis of an adaptational increase in surface area.

Conclusions

1. The elongated nuclei of Brenner tumors and Walthard cell islands show abundant examples of a longitudinal marking that Varangot first described in 1938 but did not interpret correctly.

2. The nucleus is actually grooved or infolded although the appearance, as viewed, is often more like a longitudinal line or plate.

3. The frequency of occurrence of this modified nucleus varies in different tumor samples and also regionally within the same tumor.

4. Comparable nuclear deformation occurs in various cells in each of the fundamental tissue groups. It is probably commoner than is generally supposed.

5. Longitudinally folded nuclei, of the same type as those of a Brenner tumor, are frequent, for example, in Sertoli cells of the testis and in the epithelium of the rete testis.

6. An explanation of the origin of Brenner tumors and Walthard islands by relating them genetically to indifferent elements of the male type (Sertoli or rete cells), included within the ovary or its adnexa,

The present overwhelming tendency among writers on the Brenner tumor is to attribute the origin of these entities to Walthard cell islands and there let the ancestry rest (Meyer, 1932; Novak and Jones, 1939; and others). This is obviously but one step in the complete identification of antecedents. I should like to suggest here an ultimate origin that is simple and devoid of complications. This is that the common source of both the Walthard islands and the Brenner tumor is the peritoneal epithelium, be it of the serosa of the tube, or other adnexa, or of the specialized germinal epithelium of the ovary. Such a theory does not imply that a Brenner tumor cannot emerge from a Walthard island, but it does urge that it need not do so. In the near future I shall describe in detail a Brenner tumor that connects by a narrow stalk directly with the ovarian epithelium. In this specimen, there is demonstrated for the first time a gradual transformation from the cells characteristic of the germinal epithelium into those of the tumor.

5. *Functional Surface Increase.*—There is a logical and nongenetic way in which many, at least, of the folded or otherwise modified nuclear shapes can be explained. This is that they are direct functional adaptations that arise wherever the proper conditions exist to call them forth. Two kinds of conditions are known to be correlated with nuclei of atypical morphology and increased surface area. One is an unfavorable environment. Macklin (1916) found nuclear fragmentation in old tissue cultures in which the food and oxygen had become depleted and the catabolic products had accumulated, and also in those normal cultures to which a toxic constituent had been added. Similarly Lewis (1911) and Miller and Reed (1912) have demonstrated that the presence of toxins causes an increase in the nuclear lobulation of the neutrophils in the blood of man, the rabbit, and the guinea pig.

The second condition is active or forced cell metabolism. The nuclei of such cells are frequently not only of large size, but also they gain a marked increase in surface area by the formation of grooves, tubular invaginations, sacculations, lobes, or even complexly branching arms. Extreme forms are encountered in the nurse cells of some eggs and in the spinning glands of various larvae. These correlations are well recognized and may be found summarized in the authoritative reference work of Wilson (1925). Here also is discussed the importance of increased nuclear surface in relation to cell function. Regaud (1901) has traced in detail the occurrence of longitudinally folded nuclei in the Sertoli cells of the rat and has correlated their frequency with the periods of the spermatogenic cycle when the Sertoli cell is presumably most active as a nurse cell to the immature spermatozoa whose heads are buried in it. He found an incidence ranging from zero, or practically so (his Stages 1, 8 to 12), up to 23 or 42 per cent (his Stages 3 to 7). Believing this correlation to be highly significant, he renounced his earlier (1900) interpretation of amitosis to account for such nuclear shapes. Without having verified Regaud's correlation, stage by stage, I can merely add that in an examination of a cryptorchid testis of the rat and of rat testes that had experimentally been made inactive by female hormone administration, the Sertoli cells, which alone constitute the tubule lining, showed grooved nuclei only infrequently. Also in a human cryptorchid and in human testes showing great structural reduction due to advancing age or other causes, the incidence of grooved Sertoli nuclei is seemingly appreciably less than in active testes. Possibly if one were to differentiate stages in human spermatogenesis, as Regaud did for the

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A STUDY AND CLASSIFICATION OF NODULAR LESIONS OF THE FALLOPIAN TUBES

"Salpingitis Isthmica Nodosa"

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CHIARI,¹ in 1887, described a condition in which nodular or thickened areas appeared in the Fallopian tubes, chiefly in the isthmie and uterine portions. He pointed out that the nodules, located in the muscular wall of the tube, were made up of nests of glandular tissue which were sometimes connected with the lumen. Chiari named the condition salpingitis isthmica nodosa and believed it to be initiated by an inflammatory process.

The inflammatory concept of etiology has been accepted by most authors and is supported by the frequent association of the nests of epithelium with inflammatory lesions of the salpinx, and by the observation by some authors of beginning epithelization of the cavities of abscesses which have ruptured into the lumen of the tube.² Gonococci³ and tubercle bacilli^{4, 5} have been generally accepted as the organisms most frequently responsible for the inflammatory process.

Other theories of etiology have also been advanced. One group of investigators believes the nodules to be due to an abnormal differentiation of the Müllerian apparatus.^{6, 7} Another group believes that as the result of developmental defects,⁸⁻¹⁰ cells of the mucous membrane of the tubes and uterus are caught in the muscular coats of the salpinx, where they remain dormant and are of no significance unless inflammation ensues.

can be argued, but not without objection. A simpler explanation that derives the Brenner tumor from the germinal epithelium of the ovary is supported by certain unpublished, direct evidence.

7. Possible explanations of the cause of the longitudinally grooved nucleus are: (a) pressure deformation; (b) amitosis; (c) nuclear regression; (d) genetic relationship; and (e) provision of additional nuclear surface for functional reasons.

8. With respect to the nuclei of Brenner tumor cells, the pressure and amitotic hypotheses are inadequate and unconvincing. General regression, associated with senescence and degeneration, is unproved and apparently contrary to the visible evidence. Genetic relationship furnishes only a proximate and not an ultimate explanation. Increased nuclear surface is a fact, and the most stimulating explanation of this is that an active functional state of the cell is thereby subserved.

9. Although this functional correlation is well established for certain kinds of nuclei with increased surface, it is not known that it holds for all. The extremely high incidence of folded nuclei in a Brenner tumor demands an explanation, but knowledge of the nature and degree of functional activity in this tumor lags.

10. From the foregoing analysis, therefore, one can at present only suggest the possibility of hitherto unsuspected functional potentialities in the Brenner tumor cell. The possibility of estrogenic output requires further attention in view of the author's unpublished evidence of the direct origin of a Brenner tumor from the germinal epithelium of the ovary.

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TABLE I. ANALYSIS OF 208 PATIENTS WITH SALPINGITIS NODOSA ACCORDING TO AGE AND COLOR

AGE RANGE IN YEARS	COLORED		WHITE		TOTAL NO.
	NO.	%	NO.	%	
15-19	6	3.2	1	4.7	7
20-29	47	25.1	9	43.0	56
30-39	99	52.9	5	23.8	104
40-49	30	16.0	6	28.5	36
50-55	4	2.1			4
Unknown	1	0.5			1
Total	187	99.8	21	100.0	208

TABLE II. ANALYSIS OF 329 NODULES OF FALLOPIAN TUBES CLASSIFIED ACCORDING TO TYPES OF LESIONS AND RACIAL INCIDENCE

GROUP	SUBTYPES		COLORED		WHITE		TOTAL	
			NO.	%	NO.	%	NO.	%
I	Diverticu- losis	Diverticulosis vera	59	19.9	5	15.1	64	19.4
		Diverticulosis with fibrosis	133	44.9	10	30.3	143	43.5
		Diverticulosis with leu- cocyctic infiltration	26	8.8	9	27.3	35	10.6
		Diverticulosis with in- tramural abscess	20	6.8	5	15.1	25	7.6
		Diverticulosis with foam cell infiltration	2	0.7	-	-	2	0.6
		Total of Group I	240	81.1	29	87.8	269	81.7
II	Inflamma- tory lesions without diverticu- losis	Intramural fibrosis	20	6.8	1	3.0	21	6.4
		Intramural abscess	5	1.7	1	3.0	6	1.8
		Tuberculosis	4	1.3	1	3.0	5	1.5
		Intramural foam cell infiltration	2	0.7	-	-	2	0.6
		Intramural choles- teatoma	2	0.7	-	-	2	0.6
		Intramural leucocyctic infiltration	1	0.3	-	-	1	0.3
		Total of Group II	34	11.5	3	9.0	37	11.2
III	Endometriosis		21	7.1	1	3.0	22	6.7
IV	Intramural carcinoma		1	0.3			1	0.3
	Total of all groups		296	100.0	33	99.8	329	99.9

third.¹⁴ Large nodules were found almost exclusively in this area; smaller lesions were occasionally found in the ampullary portion.

Some of the nodules were distinct, rounded masses which involved a single portion of the wall. The majority, however, were represented by focal, fusiform swellings which involved the entire circumference of the tube and frequently were demonstrated better by palpation than by inspection. The nodules were usually firm or hard in consistency, and presented smooth, regular surfaces, although occasionally larger nodules showed surface irregularities. The serosal surface was smooth and rarely showed local adhesions. When adhesions were observed, they usually were part of a generalized pelvic inflammation and did not seem to have originated in the region of the nodules.

The color of most nodules was not different from that of the adjacent, nonnodular portion of the tube. Some of the larger nodules, however, were pale or even translucent, and some were yellowish white or brownish yellow.

Some authors^{5, 11} conclude that two types of nodularities, due to epithelial nests, can be distinguished. In one type the wall shows epithelial nests which most authors call inclusions, although some investigators^{1, 5, 12, 13} have demonstrated that they are connected with the lumen of the tube and with each other. This lesion is generally considered to be the result of inflammatory processes. The other type is due to the extension of endometrium into the wall of the tube and is not associated with inflammation. The weight of opinion suggests that the inclusions of tubal epithelium are more common and that they can readily be distinguished from endometriosis.

The purpose of this paper is to describe the various histologic pictures found in a series of nodular lesions of the tube and to suggest the possible pathogenesis of the conditions. In addition we wish to emphasize that the epithelial nests which appear to be inclusions are, in reality, diverticula.

The literature and controversial issues concerning the pathogenesis of salpingitis nodosa have been summarized by Rabinovitz¹³ and Lehwirth.¹¹

Materials and Methods

The material for this study was derived from the Fallopian tubes surgically removed from 208 patients treated in the Charity Hospital of Louisiana at New Orleans. Only tubes with gross or microscopie thickening of the wall were selected, and a total of 329 nodules were studied. This number does not represent all of the nodules in the tubes.

Gross and microscopie studies of all of the tubes were made. Intraluminal injections of thorotrast under slight pressure were made into approximately 50 tubes, which were then fixed in formalin and examined roentgenologically. Serial sections were made of twelve nodules.

A cast of the lumen and two of its diverticula was constructed from a segment of the isthmie portion of one tube. This was made by projecting the images, magnified 25 times, of the serial sections of one nodule upon paraffin-beeswax plates of uniform thickness and tracing the outlines of the spaces with a teasing needle. Areas representing the spaces were then cut out and the plates fitted together serially. Plaster of Paris, re-inforced with tie wires and brass rods, was used to make the cast.

Intraluminal injections of a solution of liquid rubber were made of 25 tubes, but the method did not prove satisfactory for our purpose.

Results

Age and Color Incidence.—Of the 208 patients with salpingitis nodosa, 187 were colored and 21 were white, a ratio of 8.9 to 1 (Table I). The largest number of the colored patients (52.9 per cent) was in the fourth decade of life, whereas the largest number of white patients (43.0 per cent) was in the third decade. In the colored group the incidence dropped rather sharply in the decades above and below the fourth; in the white patients a relatively high incidence of the disease was found in the fourth and fifth decades, 23.8 per cent and 28.5 per cent, respectively.

Gross Description of the Lesions.—The majority of the lesions were found in the isthmie portion of the tube, that is, the medial constricted

thickening could be seen or palpated, very early lesions were frequently found in the routine microscopic sections of the isthmus of tubes which showed other evidences of inflammation.

Classification of the Lesions.—The lesions were classified into four major groups (Table II). Groups I and II were subdivided because of the differences in the cytologic factors which accounted for the nodularity.

Group I. Diverticulosis (81.7 per cent).—Before the various subtypes are described, a general description of diverticulosis will be presented.

Collections of simple columnar or pseudostratified epithelium, arranged to form irregular alveolar spaces, were included in the muscular coat of the tube (Figs. 1 and 2). In most instances the cells were indistinguishable from those of the tubal mucosa; some were ciliated. The larger spaces were often lined by somewhat flattened cuboidal epithelium.



FIG. 1. Section of a Fallopian tube injected with thorotrast. The diverticula are in the isthmus at the right. Note the variation in size.

The character of the inclusions of epithelium varied. Sometimes the alveoli were collected in small multiple foci, each of which was separated by a distinct mass of muscle fibers. In other cases there were innumerable epithelial-lined spaces scattered uniformly throughout the muscle wall, from the mucosa to the serosa, and separated from each other by only a small amount of muscle tissue. In this type of lesion the entire wall was converted into a honeycomb of spaces in which the lumen of the tube could sometimes be identified only by a regular circular arrangement of the muscle around it.

The alveolar spaces varied both in shape and size. Generally speaking, the smaller spaces were irregularly rounded; the larger ones frequently assumed irregular shapes, with angularities and bulbous dilated areas. Some spaces had slitlike lumina; others, which were markedly dilated and cystic, measured as much as 0.4 cm. in diameter.

Often the spaces were completely empty. Sometimes they contained a homogeneous or a granular coagulum. Other spaces were filled with either desquamated epithelial cells or macrophages with or without phagocytosed brown pigment. Very occasionally a purulent exudate filled the lumen.

Many of the lesions were multiple, and in the tubes which were extensively involved, the wall often had a beaded appearance. Counts of the number of lesions present, as indicated by palpation and inspection, were frequently proved inaccurate by later roentgenologic studies, which almost invariably increased the number counted.

Some nodules measured as much as 2.5 cm. in diameter. In other cases, the thickening was so slight that its presence could be definitely established only by microscopic examination. Even though no focal



Fig. 1.—Cross section through the isthmus of a Fallopian tube showing an early lesion of diverticulosis. Note the spaces, lined by ciliated columnar epithelium, in the muscle coat directly beneath the mucosa. Hematoxylin and eosin; $\times 108$.



Fig. 2.—Cross section through the isthmus of a Fallopian tube showing diverticulosis vera. Note the irregular epithelial-lined spaces lying between the muscle fibers of the wall of the tube. Hematoxylin and eosin; $\times 100$.

of the lumen of the tube. Small collections of tubules were unconnected with the lumen.

The subtypes were classified as follows:

1. *Diverticulosis Vera (19.4 per cent) (Fig. 2).*—In this lesion, diverticula were solely responsible for the nodularity, although in some instances the connective tissue and muscle directly beneath the mucosa was infiltrated with a few inflammatory cells.

2. *Diverticulosis With Fibrosis (43.5 per cent).*—In addition to diverticula, fibrosis of the muscularis of the tube was observed in this lesion. In many instances a few chronic inflammatory cells were also present. The relative proportions of diverticulosis and fibrosis varied greatly. It was apparent in all instances that the fibrosis contributed to the nodularity.



Fig. 6.—Cross section through the isthmus of a Fallopian tube at the point of occlusion of the lumen. Note the remnants of the mucosa embedded in scar tissue infiltrated with lymphocytes. Portions of diverticula are represented by the large epithelial-lined spaces which lie in the muscle coat.

3. *Diverticulosis With Leucocytic Infiltration (10.6 per cent).*—In this lesion diverticulosis was accompanied by leucocytic infiltration of the wall of the tube. Slight fibrosis of the muscularis was usually present. The relative proportions of diverticulosis and leucocytic infiltration varied greatly. Most of the inflammatory cells were lymphocytes which were diffusely scattered or distributed in a focal manner. Lymph follicles with well-developed germinal centers were occasionally noted in the dense cellular infiltrations which frequently appeared beneath the mucosa. Macrophages were not infrequently present in the form of foam cells. Plasma cells, eosinophiles and neutrophils were occasionally noted.

4. *Diverticulosis With Intramural Abscess (7.6 per cent) (Fig. 8).*—Chronic intramural abscess was the most prominent feature of this lesion. Spaces lined with epithelium often were not numerous, and in some lesions only fragments of epithelium were present in the abscesses.

Hypertrophy of the muscle tissue was observed, although the degree and frequency of this change, as related to the extent of epithelial invasion, was difficult to determine.

The true nature of these spaces was not evident until they were visualized with x-ray following the instillation of thorotrast into the lumen of the tube. The roentgenograms (Fig. 3) confirmed the variations in the size, shape, number, and distribution of the diverticula observed in single paraffin sections. In some films only a few small, budlike outpouchings from the lumen were observed. In others the maze of opaque channels in the wall of the tube was so great that the lumen of the tube was almost completely obscured (Fig. 4). Often the lumen was narrowed in the area of the diverticulosis, and occasionally was completely occluded distal to it (Figs. 5 and 6).



Fig. 4.—Roentgenogram of a Fallopian tube injected with thorotrast. Grossly, the isthmus was markedly thickened and nodular. The diverticula are so numerous that the lumen is only faintly visible as it passes through the nodule.

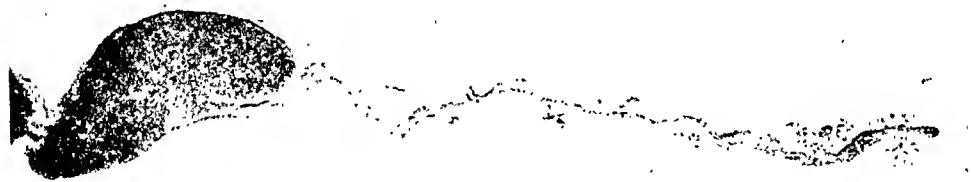


Fig. 5.—Roentgenogram of a Fallopian tube injected with thorotrast. The isthmus shows numerous diverticula, some of which were not evident grossly. The lumen of the tube is occluded medial to the last nodule on the right. The plaster of Paris cast was constructed from this nodule.

Single and serial paraffin sections, made from the tubes injected with thorotrast, showed the granular brownish precipitate of the opaque substance in the lumen of the tube and in the majority of the epithelial-lined spaces in the wall. Scattered spaces, however, remained unfilled.

Serial sections of the tubes thus studied confirmed the x-ray findings and showed that the spaces were part of a complicated intercommunicating network making up one or more diverticula.

The plaster of Paris cast (Fig. 7) prepared from serial sections of two diverticula in one tube, also confirmed the x-ray studies. Each of the diverticula was attached to the lumen of the tube by a single rather broad connection. Beyond these attachments a complicated anastomosing network of tubules ramified through the wall of the tube. The long axis of these tubules was, in general, parallel to the long axis



Fig. 8.—Cross section through the isthmus of a Fallopian tube showing diverticulosis and intramural abscess. The diverticulum arises from the lumen of the tube at the left. The edge of the abscess wall is at the upper right. Hematoxylin and eosin; $\times 108$.



Fig. 9.—Cross section through the isthmus of a Fallopian tube showing intramural fibrosis. Most of the muscle is replaced by scar tissue. Lymph follicles are present. Hematoxylin and eosin; $\times 125$.

Single or multiple abscesses were present in single nodules, and the shape of some of the larger abscesses suggested that they had been formed by the coalescence of smaller single abscesses. Our material did not show an abscess draining into the lumen of the tube, such as other observers have described.

5. *Diverticulosis With Foam Cell Infiltration (0.6 per cent).*—In this lesion the wall of the tube showed large focal accumulations of foam cells in addition to the diverticula.



Fig. 7.—Plaster of Paris cast of one nodule in the isthmus of a tube. The lumen of the tube is represented by the central large solid shaft. Two diverticula are present, one on either side of the lumen. Each communicates at right angles with the lumen at the sites of the arrows. Note the variation in size and shape of the intercommunicating tubules. In general, the long axis of each tubule runs parallel to the long axis of the lumen. Some tubules do not communicate either with other tubules or with the lumen. Those at the lower right are from another diverticulum. $\times 25$.

present in the wall of the tube (Fig. 10). All lesions in this group were located in the isthmie portion of the tube, and most of them were very near the uterine portion. In some cases morphologic variations compatible with the cyclic changes observed in normal endometrium were found in both the glands and stroma. One tube in this group was studied roentgenologically. It presented a communication between the glandular spaces of the nodule and the lumen of the tube.

Group IV. Intramural Carcinoma (0.3 per cent).—This lesion was a metastatic carcinoma of the endometrium. The nodule consisted of an isolated mass of neoplastic cells in the wall of the isthmie portion of the tube.

Comment

Diverticula, alone or in association with acute or chronic inflammatory lesions, accounted for 81.7 per cent of the nodules. Even though all of the epithelial "inclusions" which were observed on microscopic examination were not proved to be diverticula by x-ray or serial section, we feel justified in classifying them as such because of the consistency of this finding in those tubes which were examined by these methods. Less frequent causes were inflammatory lesions alone, endometriosis, and metastatic carcinoma.

The disproportionately high incidence of the various forms of diverticulosis and of inflammatory lesions with diverticulosis in colored as compared to white women was a true disproportion. During a ten-year period, of which the period included in this investigation was a part, the ratio of white to colored gynecologic admissions to Charity Hospital was approximately 1 to 1¹⁶ (52.01 per cent to 47.99 per cent, respectively), whereas the proportion of white to colored cases of tubal nodularity was approximately 1 to 9.

One reason for the preponderance of these types of lesions in the colored race is that the colored females admitted to the Charity Hospital gynecology service frequently have gonorrheal salpingitis, a disease which is closely related to nodular lesions of the tube. Another reason is that more tubes were removed from colored than from white patients because colored women have leiomyomas of the uterus approximately eight times more often than do white women,¹⁶ and salpingectomy is often done in combination with hysterectomy for this condition.

The highest incidence of tubal nodularity in white women was in the third decade, and that of colored women was in the fourth decade of life (Table I). The explanation of this lies in the fact that many of the tubes from the colored patients had been removed not because of tubal disease, but during the course of a hysterectomy for uterine leiomyomas, a disease which commonly manifests itself in the Negro during the fourth decade of life.¹⁶ On the other hand, many of the tubes from white patients were removed because of primary tubal disease, which manifests itself at an earlier age. That these conditions were factors in the age distribution is supported by the fact that diverticulosis in

Group II. Inflammatory Lesions Without Diverticulosis (11.2 per cent).—1. *Intramural Fibrosis (6.4 per cent) (Fig. 9):* All degrees of scarring of the muscle, plus a mild degree of chronic inflammation, were noted. Occasionally foci of lymphocytes were present. This lesion apparently represented the end stage of an inflammatory process.

2. *Intramural Abscess (1.8 per cent):* These lesions resembled those described in diverticulosis with intramural abscess except for the absence of epithelial-lined spaces.

3. *Tuberculosis (1.5 per cent):* These lesions presented the usual histologic picture of tuberculosis.

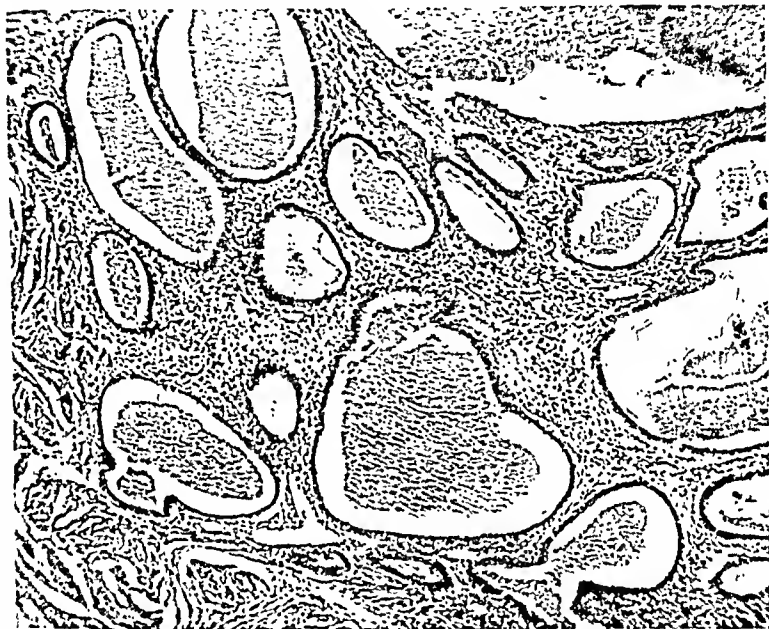


Fig. 10.—Cross section through the isthmus of a Fallopian tube showing endometriosis. Note the typical endometrial stroma and glands. The granular material in the lumina of the glands is thorotrast. Hematoxylin and eosin; $\times 75$.

4. *Intramural Foam Cell Infiltration (0.6 per cent):* This lesion was found in two cases. One case showed a widespread, diffuse macrophagic infiltration of almost the entire wall of the tube. Most of the macrophages were of the foam cell type. The other case showed large focal accumulations of foam cells about a small focus of necrotic tissue in the wall of the tube.

5. *Intramural Cholesteatoma (0.6 per cent):* This lesion consisted of a collection of granular necrotic amorphous material in which many cholesterol clefts were present. There was a zone of mild chronic inflammatory reaction about the necrotic material.

6. *Intramural Leucocytic Infiltration (0.3 per cent):* This lesion was characterized by marked diffuse infiltration of the wall with round cells, most of which were lymphocytes. No necrosis and very little fibrosis were present.

7. *Lymphogranuloma Venereum:* A case in which lymphogranuloma inguinale was identified as the cause of tubal nodularity has previously been reported¹⁵ and is not included in this series.

Group III. Endometriosis (6.7 per cent).—Glands similar to uterine glands and a stroma indistinguishable from endometrial stroma were

We are indebted to Drs. Robert Rose, Norman C. Woody and Charles Wise, who prepared the cast of the Fallopian tube while they were fourth year students in the School of Medicine at Louisiana State University.

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FETAL TACHYCARDIA DURING LABOR*

A Fallible Sign of Fetal Distress

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MOST obstetricians believe that an unusually rapid fetal heart rate is a sign of distress in the infant. Rates of 160 beats or more per minute are considered with anxiety, whereas rates between 180 and 200 are considered with alarm. Because of this fear it is common practice to deliver these infants, usually by some hazardous operative procedure, as quickly as possible. Babies born of such labors are sometimes asphyxiated, sometimes injured, and sometimes dead. It is reasonable to suppose that the distress of many of these fetuses takes place at the time of delivery and not at the time of the tachycardia.

This report deals with a group of infants that survived periods of tachycardia without specific treatment and without evidence of asphyxia or injury at birth.

Of historic interest is von Winckel's¹ report of 1903, as he was one of the first to advise immediate delivery of a fetus whose heart rate exceeded 160. This policy was widely accepted and has become a principle of obstetric teaching. The universal appeal of a mathematical method for medical practice probably contributed toward the perpetuation of this teaching.

*Aided by a grant from the Wisconsin Alumni Research Foundation.

the colored race was frequently accompanied by fibrosis, indicating that the lesions were of long duration, whereas diverticulosis in the white race was frequently associated with suppurative inflammatory lesions, indicating that the lesions were of more recent origin. The age incidence, therefore, seemed to depend more on the circumstances which permitted us to examine the tubes than on any fundamental difference in the disease process in the two races.

The pathogenesis of the most common lesion, diverticulosis, is of great interest. The frequent association of inflammatory processes with the diverticula seems to leave little doubt that inflammation is an etiologically related lesion. This thesis is supported by the observations of other workers, who have described epithelization of the cavities of abscesses which have ruptured into the lumen of the tube. It is also possible that deep ulcers of the mucosal surface may allow the epithelium to gain access to the muscular coat. From an anatomic standpoint the absence of a muscularis mucosa in the Fallopian tube makes the muscular coat more readily accessible to invasion by the tubal epithelium.

Once the epithelium is established in the muscular coat, whatever the means of invasion may be, it apparently proliferates slowly and invades the muscular tissue widely. The proliferation of the epithelium may be accounted for in large part by nonspecific stimuli arising in association with the reparative and regenerative processes which occur in chronically inflamed tissue. In addition, muscular contractions of the tube may tend mechanically to push the acini between the muscle fibers. It is possible, finally, that cyclic hormonal influences may cause proliferation of the epithelium; invasion of the muscular coat of the uterus by uterine glands has been described in mice receiving large doses of estrogens.¹⁷

Whatever the exact mechanism of pathogenesis may be, it is interesting to note that similar epithelial invasions are found in the muscular wall of the chronically inflamed gall bladder, the anatomic structure of which is similar to that of the Fallopian tubes.

Summary

1. Three hundred and twenty-nine nodules in the walls of Fallopian tubes of two hundred and eight patients were studied.
2. Eighty-one and seven-tenths per cent of the nodules were due to diverticula of tubal epithelium alone or in association with acute or chronic inflammatory lesions. We have suggested the term diverticulosis of the Fallopian tubes for these types of lesions.
3. Eleven and two-tenths per cent of the nodules were due to inflammatory lesions without diverticulosis; six and seven-tenths per cent were due to endometriosis and three-tenths per cent were due to metastatic carcinoma of the endometrium.

by auscultation and when the recorded rate was obtained at the end of the interval between contractions. Observations which failed to meet these standards were considered inadequate and were excluded.

It must be noted that gross inaccuracies are common when rates faster than 175 beats per minute are counted by auscultation. Extensive experience and the use of a stop watch may be combined to improve the accuracy of counting, but rates obtained by use of an ordinary watch for short intervals of time are worthless for research purposes. Accurate graphic recording of the rate obviates most difficulties, hence in these studies recordings were made with the Endoecardiograph. This is a device which produces a phonocardiogram.⁸

Results

Incidence.—Of the 250 patients studied 58 exhibited fetal heart rates in excess of 160 (Table I). Table I shows the infrequency of persistent tachycardia, and it should also be noted that rates above 180 are rarely observed. On two occasions only have rates above 190 been recorded; one was 210 and one was 214 (Fig. 1). Further analysis of incidence according to period of labor indicates that seven of the persistent class

TABLE I. INCIDENCE OF FETAL TACHYCARDIA IN 250 DELIVERIES

	NO. OF CASES	PER CENT
Persistent* (Maintained for 20 min.)		
Rate above 160	6	2.4
Rate above 170	5	2.0
Rate above 180	3	1.2
Rate above 190	0	
Total	14	5.6
Transient (Not maintained 20 min.*)		
Maximum rate between 160-169	29	11.6
Maximum rate between 170-179	9	3.6
Maximum rate between 180-189	6	2.4
Maximum rate over 190	0	
Total	44	17.6
Grand Total	58	23.2

*Rates may have been higher for a short time but never lower. Thus, two infants exhibiting rates of 210 and 214 were included in this group.

and 20 of the transient class were found in early labor, a frequency of approximately 50 per cent. Six alone (Figs. 2 and 6) of the persistent class and two of the transient class had rates in excess of 160 at the last observation possible, which was a minute or two before delivery. The remainder of the rapid rates were observed at a time between the period of early labor and delivery.

Asphyxia.—Our criteria of asphyxia are stringent and have been stated elsewhere.⁹ Briefly, mild asphyxia indicates that spontaneous respirations are delayed more than a minute after birth and without signs of oxygen want; moderate asphyxia indicates apnea, cyanosis and need of resuscitative methods while severe asphyxia indicates apnea, shock, severe oxygen want, and prolonged need of resuscitative methods.

Of the 14 classified as persistent fetal tachycardia, 12 breathed spontaneously within thirty seconds after delivery, one breathed spontaneously within ninety seconds and was called mildly asphyxiated. This mildly asphyxiated infant was a first born weighing 10½ pounds; a delay of five minutes was incurred during delivery of the shoulders

The research of Baumm² corroborated von Winckel's opinion. Baumm considered fetal tachycardia during labor as most dangerous and almost certainly indicative of intracranial hemorrhage. He even went so far as to state that efforts of delivery were useless once tachycardia had appeared. These opinions were made after autopsy of 11 infants had revealed intracranial hemorrhage, and after obstetric records had indicated tachycardia during labor. The report also stated that most of the labors were arduous and that 2 of the 11 were terminated by difficult forceps delivery. His conclusion that a fetal heart rate which increased to 160 or 170 during labor was indicative of intracranial hemorrhage seems unjustified.

One of the first to disagree was Bartholomew³ who, in 1925, said that rapid rates were not serious and moreover that they were infrequently observed. Freed⁴ found 8 fetuses with tachycardia in 500 labors; no more than two of the 8 infants were asphyxiated. Richardson⁵ was able to predict impending fetal distress due to separation of one-fourth to one-half of the placenta by an acceleration of the fetal heart rate; if further separation took place, the tachycardia was replaced by bradycardia. Rates from 160 to 180 were not regarded seriously by King,⁶ and those over 180 were not considered dangerous unless accompanied by strong uterine contractions.

Baumm² was aware of the frequency of rapid fetal heart rates during pregnancy and early labor and considered them to be unimportant, a contrast to his belief about tachycardia during active labor. Recent studies by Sontag and Newberry⁷ indicate that three-fourths of all patients have fetal heart rates of 160 or over without evidence of fetal distress at some time during the last two months of pregnancy.

Custom has given a figure of 160 as the upper limit of a normal fetal heart rate. I shall continue this usage to the extent that all rates over 160 are considered rapid, but this abnormality need not imply distress or danger. For convenience, two artificial classes have been created, transient fetal tachycardia and persistent fetal tachycardia. An arbitrary time limit of twenty minutes separates the two classes. Experienced observation soon reveals that transitory tachycardia is common, persistent tachycardia uncommon. Henceforth in this publication a transient fetal tachycardia indicates a rate of 160 or more beats per minute obtained by a count of thirty seconds but with a duration of less than twenty minutes, whereas a persistent tachycardia indicates that the rate exceeded 160 for twenty minutes or longer. An increase of this arbitrary period of time from twenty to thirty minutes or a reduction of the period to fifteen minutes would have resulted in small and unimportant changes in the proportions of transient and persistent fetal tachycardia.

Methods and Material

Data were obtained by extensive observations of 250 women throughout labor. The findings were considered adequate only when the study began early in labor, when the rate was observed frequently during early labor and continuously during the late first stage and second stage of labor, when the rate was calculated from graphic records as well as

because of dystocia. One infant, presenting by breech, was delivered by craniotomy after it had died during delivery because of cephalopelvic disproportion. This death was unrelated to the tachycardia and shall be excluded from further consideration.

Two moderately asphyxiated infants were delivered from the group of 44 classified as transient fetal tachycardia. One was born by a difficult forceps delivery and the other was depressed because the mother had received $7\frac{1}{2}$ gr. of pentobarbital sodium as an hypnotic agent during labor. There were no severely asphyxiated infants.

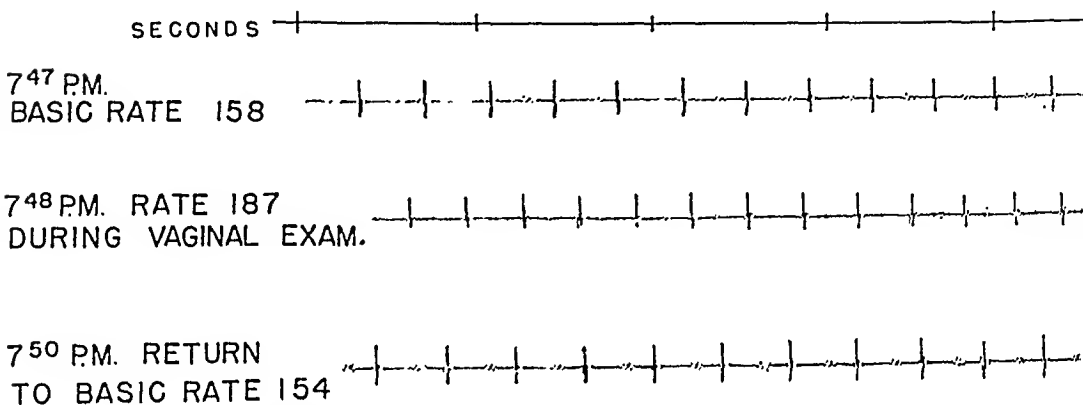


Fig. 4.—Record shows fetal tachycardia occurring during vaginal examination in the second stage of labor. The transient acceleration was associated with palpation of the fetal head. This procedure may also produce a temporary slowing of the fetal heart rate.

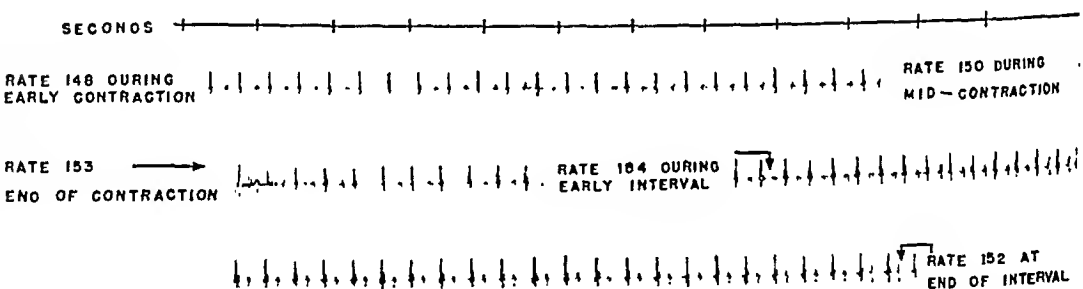


Fig. 5.—The rate was stable at about 150 during the entire contraction but quickly accelerated to 184 in the early interval. A gradual slowing brought the rate again to normal during the interval. Tachycardia immediately after a contraction is unusual.

Returning for the moment to those infants of both classes who had tachycardia just before delivery, the data indicate that one was mildly asphyxiated, the five others were normal. The circumstances of this mild asphyxia were told in a preceding paragraph.

Death.—There was but a single death, a stillbirth which was delivered by craniotomy. There were no neonatal deaths.

Etiologic Factors.—To determine the cause of fetal tachycardia has not been the purpose of this report, yet careful study of the state of labor at the time of tachycardia gives data worthy of record and thought. Table II lists the likely causes of transient fetal tachycardia. No cause was found for half of these rapid heart rates. Of the remainder most were due either to fetal activity or to pressure on the fetal head (Figs. 3, 4, and 5).

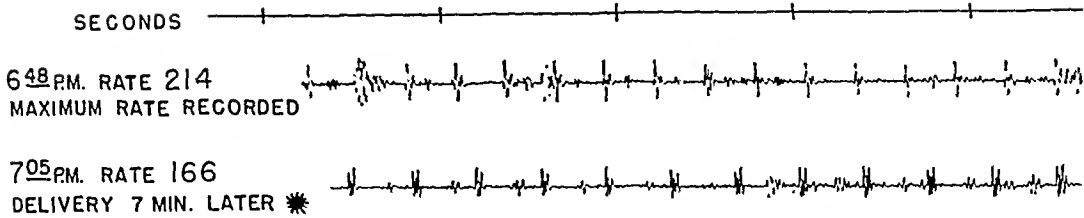


Fig. 1.—The most rapid rate recorded. Note that the rate decreased spontaneously to 166. There was no evidence of fetal distress or neonatal asphyxia at birth.

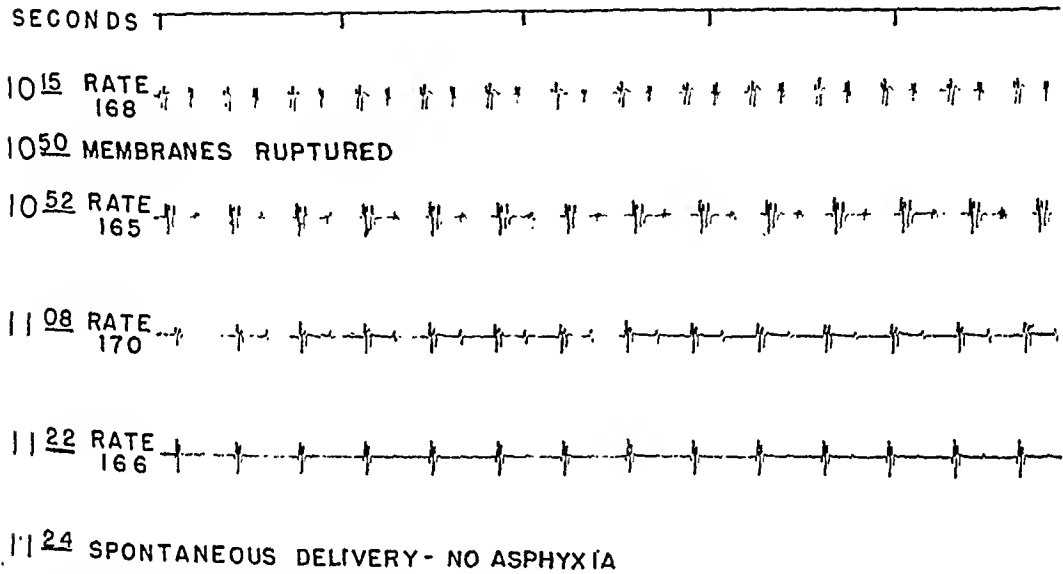


Fig. 2.—This record illustrates untreated persistent fetal tachycardia. The infant was normal at birth although the heart rate had exceeded 160 for sixty-nine minutes before delivery.

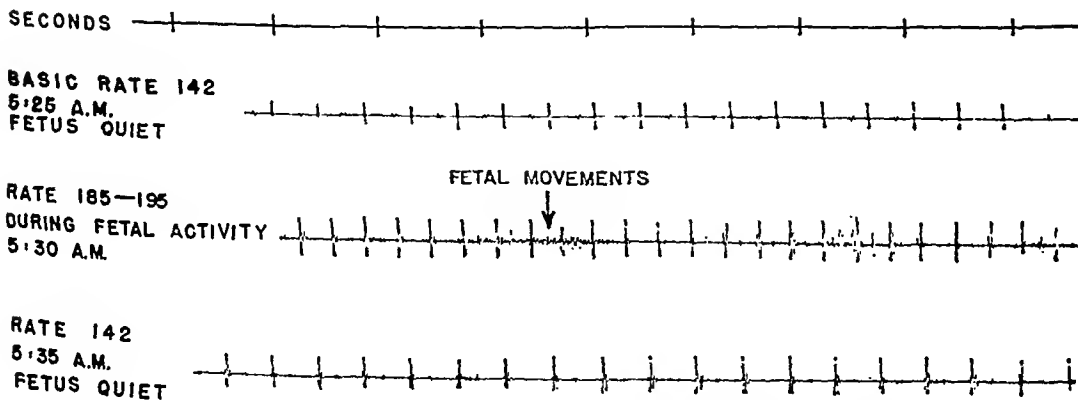


Fig. 3.—Fetal activity was followed by tachycardia, then the rate returned to normal during quiescence. Note that the fetal movements were clearly recorded during the period of activity. This record was made early in labor.

TABLE II. FACTORS CONCERNING THE ETIOLOGY OF TRANSIENT TACHYCARDIA

Fetal movements and activity	5 cases
Application of forceps	2 cases
Pressure of fetal head against perineum	7 cases
Uterine contractions	6 cases
Stimulation from rectal or vaginal examinations	2 cases
Unexplained	22 cases
Total	44 cases

It is apparent that fetal activity, application of forceps and vaginal examination played little part in the etiology of persistent tachycardia, because these factors did not persist for twenty or more minutes. It is difficult to determine any cause for the persistent class (Fig. 6). Nine of the 14 infants of this class developed tachycardia after the membranes had ruptured. In three infants only was the umbilical cord around the neck. There were a few other less likely factors but discussion of such minor details would be fatuous.

Thus far anoxia has been deliberately omitted from the discussion of etiologic factors. There was clinical evidence of anoxia in eight of the women. In only one of these individuals was the fetal tachycardia noted at the time of anoxia. In another infant the anoxia appeared long after the tachycardia and was wholly unrelated. In the six remaining, anoxia resulted in fetal bradycardia, the usual reaction.⁸ However, after oxygen was administered to the mother, the fetal heart rate returned to normal but then continued to accelerate and reached levels above 160 where the rate persisted for varying periods of time (Fig. 7). Continued administration of large amounts of oxygen to the mother was without effect on the fetal heart rate. Notwithstanding many attempts, at no time was it possible to reduce a rapid fetal heart rate by administration of oxygen to the mother.

Discussion

The frequency of transient fetal tachycardia contrasts with the infrequency of persistent fetal tachycardia; in this study the ratio was approximately 3:1. Sontag⁷ reported an incidence of from 72 to 76 per cent of fetal tachycardia at some time during the last two months of pregnancy. The discrepancy between Sontag's and these figures may be explained by two factors. First, there is a definite tendency for the fetal heart to beat more slowly after active labor is established.¹⁰ It is well to remember that half of our instances of tachycardia appeared early in labor. Second, I have attempted to record the basic fetal heart rate at all times; a basic rate is obtained at the end of the interval between uterine contractions and at a time when the infant is not unusually active. Continuous auscultation during the early course of labor, no doubt, would have disclosed additional instances of transient fetal tachycardia. Although these observations indicate that fetal tachycardia may occur in 25 per cent of the patients during labor; in most instances the rapid heart rate does not persist for twenty minutes. Furthermore, fetal heart rates above 200 are very rare and in my experience have always been transient.

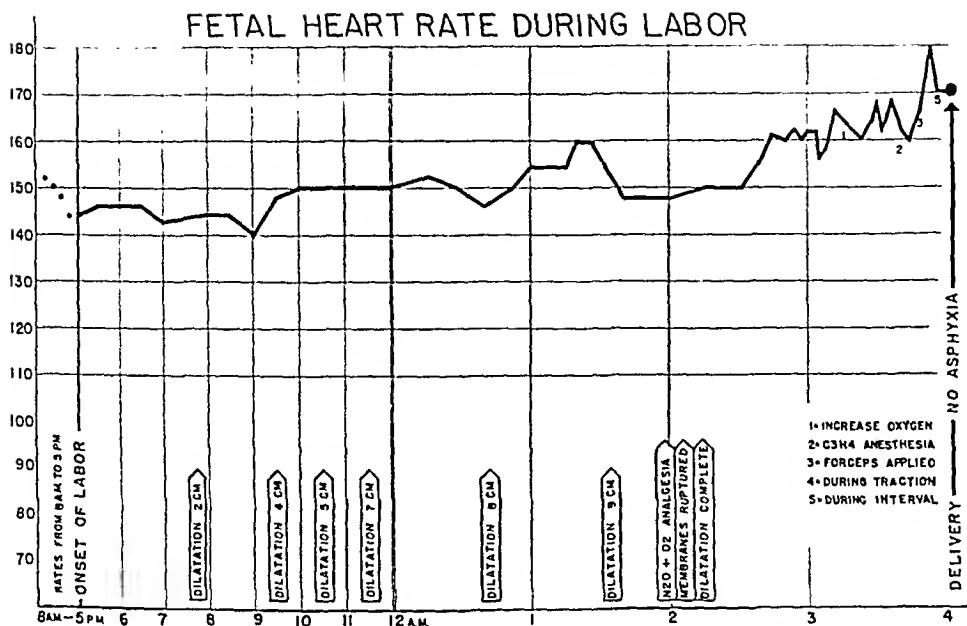


Fig. 6.—Graph of fetal heart rate throughout labor. The tachycardia appeared late in labor without apparent cause and persisted for over an hour. Administration of oxygen was without effect. Note that there was an additional increase in rate when forceps were applied. The infant was born without asphyxia.

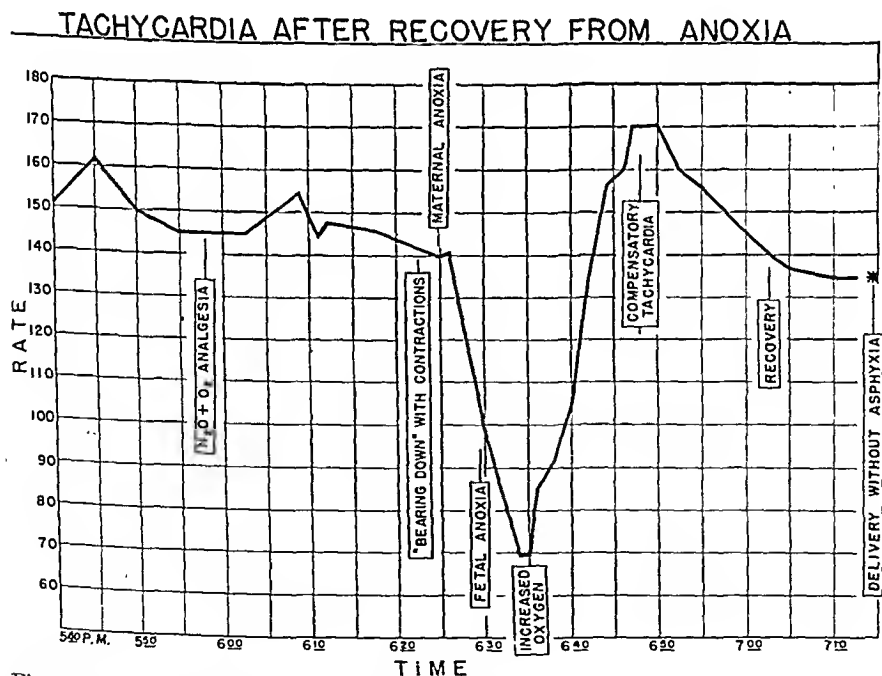


Fig. 7.—In this patient anoxia produced a slow fetal heart rate without evidence of a preliminary tachycardia. Administration of oxygen to the mother quickly corrected the fetal bradycardia. The succeeding compensatory tachycardia gave way to a normal rate after a few minutes.

contrast with the results we have had by similar treatment of slow fetal heart rates. Anoxic fetal bradycardia can be controlled quickly and effectively by administration of oxygen to the mother as long as the oxygen transportation system remains intact.

There is one association of fetal tachycardia and anoxia which is occasionally observed, a tachycardia which sometimes follows the successful treatment of fetal anoxia. The course of events has usually been as follows: First there is a period of maternal anoxia which results in the characteristic slow or irregular and slow fetal heart. When oxygen is given to the mother, the fetal heart rate returns to normal. However, instead of remaining at normal, the rate continues to increase and is finally maintained for several minutes at a high level. Later the normal rate may be resumed (Fig. 7). For lack of a better term, this fetal tachycardia has been called compensatory, as it represents recovery from a period of bradycardia. From these observations it may be assumed that occasionally a rapid fetal heart rate may indicate recovery from anoxia when the tachycardia follows oxygen therapy, a complete reversal of the concept that tachycardia usually precedes bradycardia and is a sign of anoxia and impending distress.

Summary and Conclusions

1. From careful observations of the fetal heart rate throughout labor, rates in excess of 160 were found in 58 of 250 patients. In 44 of these labors the rate was transient; i.e., persisted for less than twenty minutes. In 14 instances the rate persisted for periods longer than twenty minutes. Only two infants had rates that exceeded 190 beats per minute and these for a very short time. Rates in excess of 160 during delivery were also uncommon: Seven infants only exhibited this finding.

2. There was no evidence that tachycardia indicated fetal distress. There were but three asphyxiated infants and one stillbirth in the group studied and none could be associated with the tachycardia.

3. Fetal movements were followed consistently by tachycardia though not always to a level of 160 beats per minute. Uterine contractions, application of forceps, pressure on the fetal head during rectal and vaginal examinations, and pressure of the fetal head against the perineum were sometimes followed by tachycardia although bradycardia was the reaction more frequently observed.

4. Anoxia was not found to be a cause of tachycardia in the fetus; this is in contrast to reactions usually observed in the adult.

From the results the author cannot subscribe to the notion that rapid fetal heart rates are either common or hazardous. Dangerous and unjustified obstetric intervention has been largely responsible for the unfortunate results commonly and erroneously attributed to fetal tachycardia.

However great or small the incidence of fetal tachycardia, it is of academic interest alone so long as the fetus remains free from danger. As there was but a single death in this group of infants, a death from causes definitely apart from the tachycardia, no little doubt is raised about the hazards usually attributed to rapid fetal heart rates. Neither was there danger in the form of neonatal asphyxia, as this was found in three infants only. While fetal tachycardia might have been a sign of impending asphyxia in these three infants it is unlikely because on two occasions dystocia influenced the fetus *after* the period of tachycardia and in the remaining instance the fetus was depressed by an hypnotic drug. No infant had neonatal complications which could be ascribed to fetal distress in utero.

Clinical observations do not permit speculation about the physiologic mechanism of fetal tachycardia. Windle¹¹ has summarized excellently the meager physiologic data now available. Baumm² was one of the first to report that active fetal movements during pregnancy were followed frequently by an acceleration of the fetal heart rate, an observation recently elaborated by Sontag.¹² Such tachycardia occurs not only during pregnancy but also during labor; however, active fetal movements usually decrease as labor progresses and consequently tachycardia from such a cause is less common late in labor.

The reaction of the fetal heart to fetal activity is almost constant; in nearly every case the rate accelerates and frequently reaches a level of 160 or over. The reaction of the fetal heart to other stimuli is far less constant. Several illustrations have demonstrated fetal tachycardia from such causes as pressure of forceps, vaginal examination, uterine contractions and others, but it must be pointed out that very frequently these same causes produce a slow or irregular rate or no change at all; in fact, tachycardia is usually an exception rather than the rule.

A notion is prevalent among obstetricians, probably because of the reactions observed in the adult, that an oxygen deficiency of the fetus will produce tachycardia at first and subsequently bradycardia if the anoxia persists. This is not the usual reaction as was shown in previous studies⁸ wherein the characteristic reaction of the fetal heart to oxygen deficiency was found to be a slow or irregular and slow rate. No relationship between fetal tachycardia and anoxia could be found in this study.

It is true that occasionally an initial acceleration of the fetal heart rate has been followed by a bradycardia in the presence of anoxia. A careful study of these observations reveals that the anoxia appeared *after* the tachycardia, thus establishing a relationship by chance rather than by cause and effect. Additional evidence against the belief that fetal anoxia produces a tachycardia was obtained when administration of oxygen to the mother failed to reduce the fetal tachycardia. The inability of oxygen therapy to reduce rapid fetal heart rates is in distinct

procedure and to decrease the attendant risks of large, rapidly injected doses of the anesthetic agent.

Technique

The procedure in detail which we employed was as follows:

1. It was necessary to give the patient a satisfactory enema to avoid fecal leakage when the rectal sphincter relaxed.
2. The patient should be made to void as she would find it impossible to do so once the caudal anesthesia has taken effect.

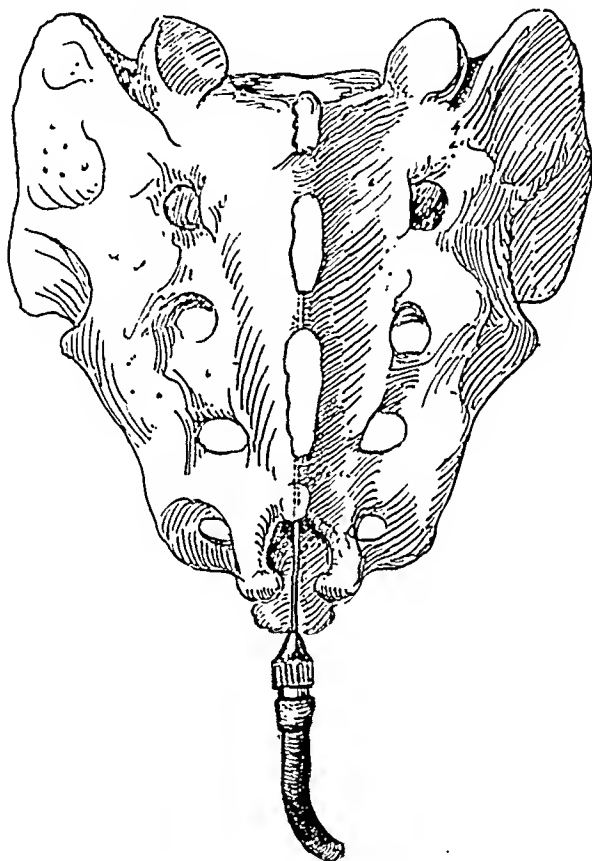


Fig. 1.—Showing insertion of needle in canal.

3. The patient was put in the knee-chest position, cleaned up with Scott's solution,* and draped.

4. The sacral hiatus was palpated, and 1 per cent procaine was injected to raise a skin wheal.

5. A 17 gauge continuous spinal needle was introduced through the wheal, and then guided into the sacral canal for a distance of about $2\frac{1}{2}$ to 3 inches (Fig. 1).

6. The patient was turned on her side and a Luer-Lok syringe was then attached to the needle and an attempt was made to aspirate spinal fluid.

*Mereurochrome, 2%, in alcohol, acetone, and water (B. W. & Co.).

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CONTINUOUS CAUDAL ANESTHESIA IN OBSTETRICS

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CAUDAL anesthesia in obstetrics was used apparently for the first time in the year 1919, but it did not make its appearance in America until 1923. Since then it enjoyed moderate popularity in this country. However, because of the element of risk, the procedure never became widespread, as safer anesthetics were available. Much of the early work was done in Baltimore and the method was used extensively in several of the larger hospitals. Baptisti¹ in 1939 reported 200 cases with excellent results. However, this method of obstetric anesthesia was discontinued throughout the city several years ago because of three maternal deaths in a total of approximately 600 cases. These deaths were all attributed to the anesthetic. Each of the deaths occurred in a different hospital after a large series of successful cases.

Very recently, Edwards and Hingson² published several papers on continuous caudal anesthesia which they used, not only for delivery, but as a means of producing a painless labor. They adapted Lemmon's⁴ method of continuous spinal anesthesia to caudal anesthesia, and obtained striking success in 65 cases with no serious complications.

We were very much impressed by this report and a decision was made to try continuous caudal anesthesia in this institution despite the unfavorable experiences previously encountered.

We made several changes in the technique described by Edwards and Hingson as we believed that these innovations would increase the safety factor. A 1 per cent procaine solution was used instead of 1.5 per cent metycaine as shorter acting and less toxic. In addition, in order to eliminate the large injected doses of the syringe method which Edwards and Hingson employed, we devised a means of giving the procaine by a continuous gravity drip. This was done to simplify the

With this method we hoped to avoid any accidents as any untoward symptoms would be detected before a large amount of procaine was introduced. It also eliminated the repeated periodic injections throughout labor and provided a means of administering a more even and regulated flow of the procaine.

Results

A total of 39 patients was given continuous caudal anesthesia, 31 primiparas and 8 multiparas. The anesthesia was started as soon as possible after admission to the hospital if regular uterine contractions could be felt. The amount of dilatation was unimportant and several patients were given the anesthesia with good results although the cervix was dilated 2 cm. or less.

In this series we had 39 living mothers and 38 living babies. The lone fetal death was a macerated fetus and no fetal heart was heard on admission to the hospital. For purposes of clarity, the first 38 cases of the series will be presented as an entity and the last will be presented in detail.

In all cases complete relief from pain was noted in from ten to fifteen minutes. Uterine contractions continued unabated, yet the patient was unaware of it. The majority of the patients would lie comfortably in bed throughout labor, either reading a magazine or conversing with their neighbors. The nursing problem, which is so important these days, was considerably lessened, as these patients required little attention. The contrast in two adjoining beds, one patient resting quietly under caudal and the other noisy and attempting to get out of bed under nembutal or paraldehyde analgesia, was most striking.

Labor was shortened with caudal anesthesia. The average length of time for the first and second stages of labor together for our eight multiparas totaled two and one-half hours. This figure was attained despite several abnormal presentations and despite extremely early administration in some cases. For the 30 primiparas, the average length of time was four hours, although one-half of the patients delivered in three hours or less from the time of administration. Several cases were successfully kept under caudal for ten hours or more, the longest being twenty hours, in which time the patient received 900 c.c. of procaine with no untoward effects. The shorter duration of labor is undoubtedly due to relaxation of the cervix and perineum.

We have found caudal anesthesia to be of particular value in dystocia cases. It practically eliminated cervical dystocia and it reduced dystocia to actual cephalopelvic disproportion. Cases of this sort could be given a thorough test of labor without fear because the patient did not become exhausted and she was able to cooperate fully with the wishes of the nurse and doctor. It was a simple matter to keep her well hydrated and fed if it was so desired.

Ten patients were delivered spontaneously and 28 required operative interference. Most of the low forceps were done electively although four were indicated. Though the caput descended to the perineal floor, the loss of the sensation of rectal pressure prevented these women from bearing down unless encouraged. This practically eliminated the possibility of precipitate deliveries in bed. When full dilatation was reached, the obstetrician had full cooperation of the patient, and she could be en-

7. If no spinal fluid was obtained, a Pilling hard rubber tubing was then connected to the hub of the needle and the needle was securely taped down in the median raphe. The patient was then allowed to turn on her back.

8. The other end of the tubing was then connected by a glass adaptor to several feet of soft rubber tubing which led to a 250 c.c. graduated cylinder containing a 1 per cent procaine solution.

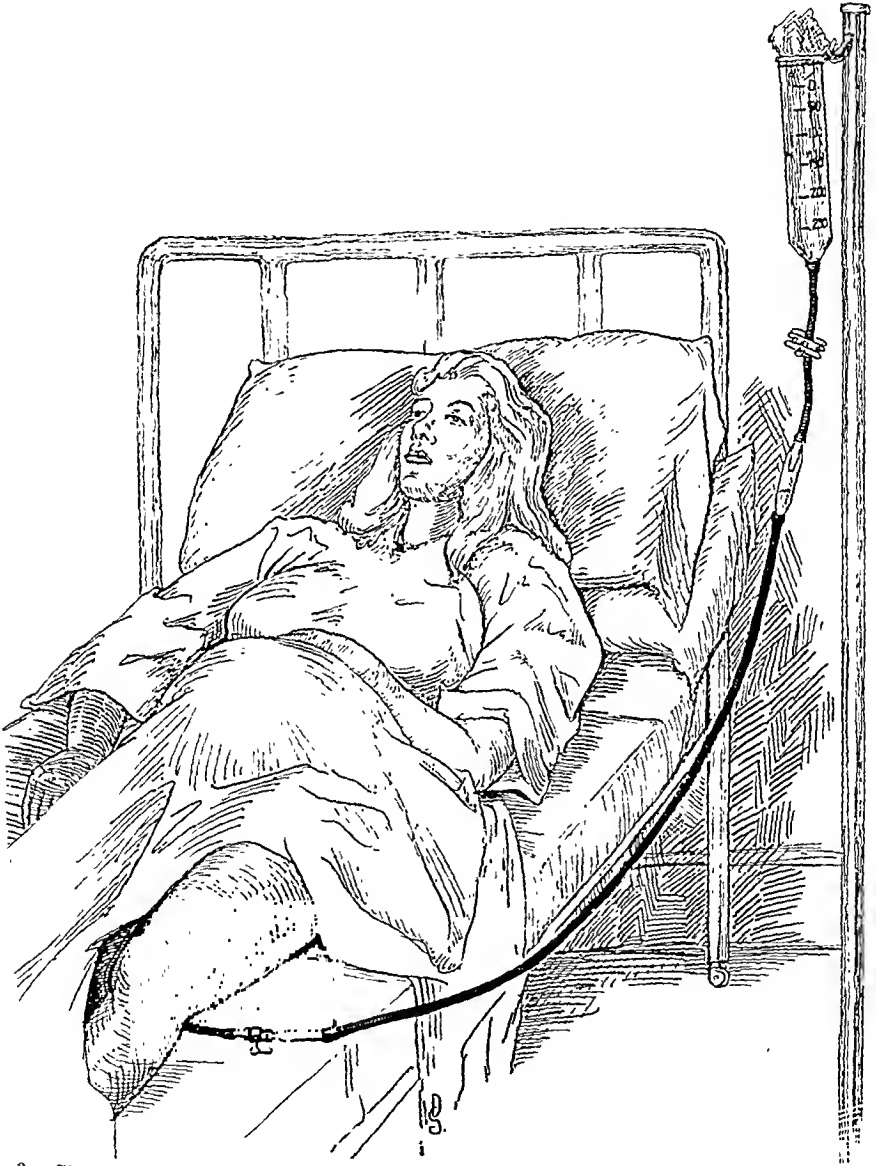


Fig. 2.—Showing position of patient, with graduate cylinder containing procaine solution, clamp, rubber tubing, and glass adaptor.

9. The cylinder was suspended from a standard at a height of from 7 to 8 feet and the stopcock released. The procaine solution was then allowed to drip at a rate of 15 to 20 drops a minute.

Cessation of labor pains occurred in ten to fifteen minutes, and the solution was allowed to flow in continuously at this rate throughout labor and delivery.

procaine by an injection with a syringe. We then hooked up our apparatus and allowed the procaine to drip in by gravity.

After five minutes the patient began to complain of some tingling in her feet, a common symptom with caudal anesthesia, but she was able to move her toes. Shortly thereafter, she suddenly lost the power of speech, became very cyanotic, and went into collapse. The patient had respiratory paralysis and her blood pressure and radial pulse disappeared. She was given artificial respiration until she could be intubated and then her respirations were maintained with oxygen through the intratracheal tube. Caffeine, coramine, and adrenalin were administered, as well as heat and intravenous fluids. Respirations were not re-established for forty-five minutes, and she had spinal anesthesia for six hours. The caudal had been discontinued at the first signs of distress, but this was not before the patient had received a total of 30 c.c. of procaine solution. The patient returned to consciousness one and one-half hours later, and ten hours later she delivered a living child. The mother and baby made an uneventful recovery, and were discharged on the tenth day in good condition.

Conclusions

Although there were no fatalities in this series, we feel that no matter how the procaine is administered, the danger of an anesthetic death is still very real. Despite its many advantages, we do not feel that continuous caudal anesthesia is a procedure to be used indiscriminately. The inherent risk of introducing the needle unknowingly into the spinal canal is constantly present. It may have a place in cases where other forms of analgesia or anesthesia are contraindicated, but we do not believe it is as safe as the anesthetics now commonly employed. We believe that its use should not become routine, particularly in smaller hospitals where a competent anesthetist is not always available to cope with the serious complications resulting from an accidental introduction of the anesthetic agent into the spinal canal.

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Ohkusa, M.: *The Role of Vitamin A, Vitamin D and Cervical Erosion*, *Jap. J. Obst. & Gynec.* 23: 39, 1941.

It is well known that vitamin A has a favorable effect by epithelization and that vitamin D is effective in certain cases of eczema. Based upon these facts Ohkusa applied vitamins A and D to cervical erosions. He combined this treatment with hot lysol douches. He maintains that vitamins A and D are effective in curing cervical erosions. This is particularly true of erosions found in acute gonorrheal infections. Cod-liver oil contains relatively small amounts of vitamins A and D, hence it is best to use a special ointment containing large amounts of these vitamins.

J. P. GREENHILL.

couraged easily to bear down. In this manner we were able to deliver 10 patients spontaneously. Three cases were breech deliveries and no difficulties were encountered.

In 35 cases no supplementary anesthesia was needed. No pain was felt despite forceps or episiotomy repairs. In three cases, a Kielland forceps for transverse arrest, an internal podalic version for a compound presentation, and a high midforceps for a persistent occiput posterior with cephalopelvic disproportion, inhalation anesthesia was utilized for delivery. The elimination of an inhalation anesthetic seemed especially valuable for the three cardiac, one nephritic, one tuberculous, four toxemic, and one upper respiratory complications which were present in this group of patients at the time of delivery.

The absence of analgesic effects upon the fetus was most striking at delivery. Except for one macerated fetus, every baby cried in less than one minute and the vast majority cried before the delivery was completed.

The difference in the amount of bleeding at delivery was also noticeable. Although no attempt was made to measure the amount of blood loss accurately, the estimated amount was far less than with inhalation anesthesia. There were no cases of post-partum hemorrhage.

Four patients with pre-eclamptic toxemias were given caudal anesthesia. In all cases some drop in blood pressure was noted. No other medication was given. Although this is inconclusive, further studies in this direction would not be amiss.

Complications

The complications that were noted in the order of their frequency were nausea and vomiting, dizziness, drowsiness, and in one instance, diplopia. These were probably mild systemic reactions to the procaine. A frequent complaint was low back pain during the first twenty-four hours postpartum which was often so severe as to require one or two doses of morphine before relief could be obtained. Two patients may have developed a neuritis, as they constantly complained of back pain during their entire hospital stay, and complete relief was not obtained until two weeks following delivery. When the series was first started 18 and 19 gauge needles were used. However, 5 of these needles broke while in use. Three were merely pulled out by the protruding fragment, but in two cases a small skin incision was made before the needle could be extracted. No needles broke after the 17 gauge needles were put in use. Despite these complications the method seemed most satisfactory, as the advantages seemed to outweigh by far the disadvantages.

Our thirty-ninth case was a 22-year-old primipara at term in early labor. She had a 3 cm. dilatation, with the cervix 50 per cent effaced and the vertex at the level of the spines. Pains were fairly strong and they recurred every three to four minutes. The fetal heart was heard in the right lower quadrant and was of good quality. The fetus was palpated in the R.O.A. position. The patient was given an enema and told to void. She was put in the knee-chest position and a 17 gauge needle was introduced into the caudal canal. Suction was made with a syringe and no spinal fluid was obtained. Unfortunately, since the patient was complaining of her pains quite frequently, we did not adhere strictly to our accepted method, and she received 10 c.c. of 1 per cent

groups of hypertensive albuminuric pregnancies (more rapidly than this can be done by any one man or clinic) and from analysis of these data in quantity to draw factual conclusions on matters pertaining to these serious complications of pregnancy now too frequently impressionistically considered because of individual limited experience with group classification. This especially in the matter of clinical prognosis; but as well such a division can serve as a sound basis for all other approach. At the Washington Conference, for example, etiologic, physiologic, metabolic, endocrinologic, and clinical discussion was so based not only by plan, but in much that was extemporaneous, instinctively. In short there is a general feeling for this sort of division among interested men at this stage in our ignorance of this subject.

Since this stated purpose is defeated *ipso facto*, unless a majority of clinic directors are in some accord, we must consider frankly the reaction in the last six years to this effort. It is clear that in order to accumulate and analyze the data and pursue allied investigation of set problems, a high degree of cooperative effort must exist between individual clinics and some properly equipped and manned bureau for collection. It is equally clear in retrospect that the American Committee on Maternal Welfare's appointed "Committee on Classification" was not equipped and manned to be the receiving body for this material and investigation. At the Washington Conference of the United States Department of Labor, Maternal and Child Health Division, Children's Bureau was stated to be so equipped and Dr. Edward Daly, Director, said the bureau was willing to act as a collection agency for these data.

We may consider briefly reaction to the attempt to acquire an acceptable tentative classification chronologically. The original paper before this Association was well received as evidenced by the appointment of a Committee on Classification. The work of this committee met with general approval as evidenced by the "acceptance in principle" of the classification in many clinics in the country. However, we left the meeting at the First American Congress with the feeling that, in general, the criticism in the discussion was not constructive and that each discussant preferred his own classification. The Washington Conference reaction was, on the whole, favorable to the work of the Committee on Classification; but failed in our opinion to take cognizance of two important points which will be discussed later. Dieckmann's *Monograph* opens with acceptance of the Committee's classification and includes a table showing the incidence of the different groups in a small number of cases from three clinics. Dexter and Weiss⁷ in their book shy away from these attempts at classification and approach the subject on the basis of different courses of hypertension in pregnancy. Tillman⁸ emphasizes the difficulties of fitting all cases to a classification but agrees with the idea that such an attempt is useful.

GROUP INCIDENCE OF HYPERTENSIVE-ALBUMINURIC PREGNANCY UNDER THE NEW CLASSIFICATION*

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IN 1936 before this Association we presented a paper entitled "Recent Experience With a New Classification of Pregnancy Complicated by Hypertension and Albuminuria."¹ The material covered the accumulation of eighteen months and hence was of value only in illustrating the groups in the classification. The purpose of the paper was to present the classification and justify its creation, and to attempt definite definitions of each group. In 1930,² before this Association, in a communication embodying an effort to correlate 1,100 cases classified crudely from the Boston Lying-in Hospital Toxemia Clinic with the Williams-Stander classification, I stated that "a cooperative study throughout the United States under a single classification is highly desirable."

Subsequent to the 1936 meeting of this Association, due to the immediate interest of Drs. Cosgrove and Adair, The American Committee on Maternal Welfare "appointed a committee to develop an acceptable classification of the toxemias of pregnancy based on available scientific and clinical knowledge of these diseases." Robert D. Mussey, Chairman of this committee, published in April, 1940, the results³ of the work of this committee.

With the publication of this report this committee ceased to function as such.

In 1939 before the First American Congress on Obstetrics and Gynecology we offered a further contribution entitled "The Classification of Hypertension and Albuminuria in Pregnancy"⁴ in which, after four years' experience, we presented a modified classification.

The purposes of the present paper are three: (1) To crystallize the product of seven years' effort for an acceptable tentative classification and to analyze future possibilities. (2) To report gross figures in the groups from the clinic of the Boston Lying-in Hospital in the five years 1935 to 1939 inclusive. (3) To consider practical limitations of these classifications, as used, especially as to subgroups.

1. We can restate the purpose of a generally used tentative classification as follows: To accumulate as rapidly as possible data on different

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If we omit mild pre-eclampsia (largely unknowns), we have

Group A	169 cases	44%
Group B	194 cases	56%

363 definitely diagnosed cases.

We have no definite statement of cross-indexing in the two groups. In this whole group the gross fetal death rate was 105 per thousand live births as against a general rate in the hospital in 1941 of 66 per thousand.

For purposes of illustration and in contrast to the above gross figures the only fairly complete report in the five-year period is given below:

Toxemia Clinic. Report of Boston Lying-in Hospital, 1939

1. The total number of patients who attended the toxemia clinic was about 10 per cent of the total patients from all the pregnancy clinics. Those who had definite toxemia of pregnancy, including cases of chronic vascular or renal disease complicating pregnancy, was 7 per cent.

The following statistics are presented:

New patients:		
Hospital	287	
Out-patient	57	
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Visits:		344
Subsequent visits		706
Follow-up visits		63
		<hr/>
Total visits		1,113
Deliveries:		
Primiparous		101
Multiparous		136
		<hr/>
		236
Toxemias classified:		
Pre-eclampsia, Grade 1 (mild)		174
Pre-eclampsia, Grade 2 (severe)		26
Eclampsia		4
Hypertension		23
Nephritis		2
Pyelonephritis		5
Cortical necrosis of the kidney		2
		<hr/>
		236

All the maternal deaths were in women over the age of thirty-five. Three of these women gave evidence, obtained at autopsy, of previous hypertensive vascular disease. It again emphasizes that caution must be exercised in this age group with vascular hypertension.

2. *Eclampsia*.—There were four cases of eclampsia with one death. Two cases were emergencies, one of which died. Three had ante-partum, and one post-partum convulsions. Two were known to have had normal blood pressures and kidney function prior to the onset of the disease and both recovered. The status of the vascular and renal systems of one patient was unknown prior to the onset of the disease, while in the patient who died autopsy revealed previous arteriolar changes.

2. We now report in summary the gross figures from the Boston Lying-in Clinic during the five years 1935 to 1939, inclusive. This material includes that in our original paper.¹

A total figure of 1,541 cases was studied, divided as follows:

Group A, i.e., Disease independent of pregnancy,	169 cases,	11%
Group B, i.e., Disease dependent on pregnancy,	1,370 cases,	89%
Total	1,541 cases,	100%

These percentages are exactly the same as in the preliminary study of eighteen months.

For better perspective, however, it should be stated that of Group B, 1,186 cases, or 86.5 per cent, were "mild pre-eclampsia," and since this group represents a little of everything and is frequently not definable at any given time, if ever, its inclusion distorts the true picture of the relative incidence of Groups A and B from a practical clinical standpoint since rarely is it of much importance in this respect.

Group B shows:

"Pre-eclampsia," mild	1,186 cases, 86.5%
"Pre-eclampsia," severe	164 cases, 12.0%
Eclampsia	30 cases, 2.2%

Total severe pre-eclampsia and eclampsia 194 cases, 14.2% of Group B

A breakdown of figures in Group A (i.e., disease independent of pregnancy) shows (and part of this is estimated due to the fact that in some years the reports did not distinguish between "chronic nephritis" and "essential hypertension"):

	1936	1938	1939
Essential hypertension			76 cases
Chronic glomerular nephritis			14 cases
Total			90 cases in which a differential diagnosis was made.

"Essential hypertension including chronic nephritis" without differential diagnosis.

	1935	28 cases
	1937	41 cases
		69
		90
		159
Pyelonephritis in all years		10
Total "Group A"		

In summary, in percentages, our five-year figures show for Group A estimated in part:

Essential hypertension	75, 80% (probably too low)
Chronic glomerular nephritis	20, 25% (probably too high)
Chronic pyelonephritis	0.6% (probably too low)

aforementioned and set the time for group indexing as of the departure of the patient from the Hospital. This time may be all right for the individual clinic although we do not believe this, but is certainly not so for group data collection, because it contradicts the principle we learned from Herriek and Tillman, namely, that some follow-up at least, and the longer the better within practical limits, is vital in grouping these patients. The Conference also dwelt at length on the loss of patients when a policy of follow-up is pursued but, as Herriek said in Washington, "It does not matter whether you get all back or not, you still have enough for a good cross section. In both private and hospital practice an adequate percentage for satisfactory study will report."

Conclusions

We therefore make the following specific recommendations.

1. That definitely defined subgroups in *Group A* be incorporated in the classification.

2. That a copy of the Proceedings of the Washington Conference on Eclampsia 1941 be made available to each clinic using the classification.

3. That arrangements be made between interested clinics and the Chairman of the so-called permanent Committee to supply the Washington Bureau with a limited round number of carefully studied cases each year on a set date, the number to depend on the size of the clinic and its personnel ability to study the cases; cases of the previous year, i.e., at the end of twelve months after hospital discharge.

4. That these reports take a set form somewhat as in our hospital report of 1939 (shown above) with somewhat similar comments but that, in addition, fetal and maternal morbidities (including specific statements on degree of prematurity in terms of weeks gestational age checked against weight); and pathologic report on all available material *including placentas*, be incorporated in each group; and a definite statement of cross-indexing, as this report does not do.

5. Thus and only thus, in our opinion, can we obtain satisfactory information with not too great individual effort and with the understanding that some clinics are better equipped and manned than others to supply data in quantity.

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3. *Fetal Deaths.*—

	GRADE 1 MILD	GRADE 2 SEVERE	HYPER- TENSIVE DISEASE	TOTALS
Delivered patients	174	26	23	223
Stillbirths	4	4	6	14
Neonatal deaths	4	1	0	5
	<hr/>	<hr/>	<hr/>	<hr/>
Total per cent	4.65	19.2	26.1	8.97
Corrected per cent:				
Stillbirths	1.72	11.5	4.35	
	1.72	.0	.00	
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	3.44	11.5	4.35	

In addition to the above there were two mothers with chronic glomerulonephritis, both of whom delivered nonviable stillbirths. Out of five cases of chronic pyelonephritis, only one baby was discharged from the hospital alive.

The fetal mortality in the toxemic group has been materially decreasing over the past five years. We believe this can be explained by two factors: first by the more frequent inductions of labor near the thirty-fifth week of pregnancy, and second, the presence of an excellent premature nursery to allow the pediatric and nursing staffs to salvage each year an increasing number of premature babies. To further emphasize this, there were only five stillborn infants in all the groups whom the obstetricians might have saved if induction of labor had been performed at an earlier date.

Comment

We have in the "classification idea" along these lines something acceptable to most obstetric clinics for present use. Its seed has now been planted for seven years; it budded with the publication in 1940 of the report of the Committee on Classification;³ it flowered mildly at the Washington Conference in 1941.⁵ As it stands now it appears to us to need still further pruning to bear its hoped for fruit.

One-half its purpose has been fulfilled; we have a common clinic language in the subject. The other half, the accumulation of data for general information, is unfulfilled.

The Committee on Classification failed to realize that for data collection purposes it is important to distinguish between mild and severe chronic glomerular nephritis and perhaps mild and severe pyelonephritis, since quite different prognoses and results exist in these subgroups, certainly in the former. (These are definitely defined in our papers of 1936¹ and 1939.⁴)

The Washington Conference, pushed for time because of the very considerable amount of ground it was attempting to cover (and an unbalanced amount of this was given to Classification discussion) planned no definite mechanism for collection of data, hastily voted to accept the Committee's Classification without consideration of the subgroups

with it. A resolution brought up for consideration by this Association, and providing the necessary means, would be a most worthy object of attack for this particular problem.

DR. A. N. CREADICK, NEW HAVEN, CONN.—There are two particular points which should be emphasized. Most clinics have associated with the obstetrician an internist and a chemist. These associates have become interested in the problem of toxemias, have criticized our clinical classification, and substituted a chemical nomenclature. However, I still think we should have associated with us medical men of the best caliber obtainable.

The second point is the use of nomenclature from a clinical point of view. At last we have begun to talk about the same things, and we had better persist in following Dr. Kellogg's nomenclature. A biochemist should be associated with this Committee, but we should continue to use the clinical nomenclature so that we will know what we are talking about.

DR. GEORGE F. PENDLETON, KANSAS CITY, Mo.—I am not satisfied with this classification. If you are going to set up a classification, it should be consistent, either clinical or anatomical. In the present terminology, for instance, we use the term eclampsia, which is a clinical entity, and then we mix this with pathologic terms as nephritis or pyelonephritis.

DR. A. J. RONGY, NEW YORK, N. Y.—Eclampsia is not a hereditary disease, but there is definitely a constitutional type, which is more prone to develop eclampsia. The experienced obstetrician in many instances should be able to anticipate the type of pregnant woman who is likely to develop toxemia in pregnancy. It is a well-known clinical fact that a woman, long-necked and long-boned, with a slightly enlarged thyroid, seldom develops eclampsia. I believe that our present knowledge of etiology of eclampsia is not sufficient to warrant any classification of the disease.

I believe that it is more important to watch these patients from a clinical standpoint and rely more on clinical symptoms than to be guided by the laboratory findings. Those patients who develop severe toxemia usually have a premonitory period and begin to complain of general malaise, loss of appetite, headaches, epigastric pain, visual disturbances, and occasionally itching of the skin, accompanied by an increase in the blood pressure and albumin in the urine. When the clinical symptoms do not improve or subside under treatment, the pregnancy will have to be interrupted.

DR. KELLOGG (closing).—I did not intend to bring up the question of what constitutes eclampsia, or suggest perfection for this classification. We would welcome a better classification from those who criticize that which we propose.

There are many subgroups, small in any one clinic or individual's experience. There is no question, for example, that there is chronic glomerular nephritis in pregnancy. There may be cases which are followed by such complete recovery that if the patient is studied with the utmost care six or eight months afterward you could not determine that she had had it. We do not yet know the prognosis for these patients in their future life as a whole or in future pregnancies. The only way to discover this is to get material for these minor groups, from a great many sources.

It is problematical as to who will carry on the work. Nevertheless, we wish to go on record at this time with this plan as desirable work for some future date.

Discussion

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—The classification of the toxemias of pregnancy is of the utmost practical importance. Patients who have had hypertension during a previous pregnancy are continually asking about the chances of going through another pregnancy satisfactorily. It is only by observing and cataloguing a large number of cases, all carefully studied and followed, that we can establish the prognosis of these patients. Dr. Kellogg's recommendation that carefully studied cases be submitted each year for analysis and review is an excellent one. It will be only a modicum of cases, however, that lend themselves to critical study, because of lack of information. Our own greatest difficulty in classifying cases of toxemia is that a history throughout pregnancy is necessary. The main dividing line used by the Committee in differentiating chronic from acute toxemia is the time factor. Do the signs develop before or after the twenty-fourth week? Very often patients develop toxemia later; and not knowing what has transpired early in pregnancy, it is impossible to classify such cases, at least on the criteria used by this classification.

In our experience, chronic hypertensive vascular disease is becoming an increasingly frequent cause of maternal death. Fifteen years ago 60 to 70 per cent of our deaths from toxemia of pregnancy were the result of eclampsia. Little by little, as a result of better prenatal care, and a better understanding of eclampsia, deaths from eclampsia have decreased to such an extent that they make up only 6 to 8 per cent of the toxemic deaths. Conversely, whereas fifteen years ago, 20 per cent of our toxemic deaths were due to chronic hypertensive vascular disease; today 70 per cent are the result of that condition. We believe, accordingly, that this group of chronic hypertensives deserves increasing attention.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—Discussion of what constitutes the several groups in a classification brought before us this morning by Dr. Kellogg is not pertinent. His plea, first of all, is for a common medium of expression. Each one of us may have our own ideas as to modifications of that medium of expression, but unless we all use the same medium we cannot get together the great mass of material which is so important. We must agree, for the present at least, on the basis which Dr. Kellogg and the Committee on Maternal Welfare have suggested. By and large it is not a bad system. I think it necessary to point out that a mere pooling of large numbers of cases will not accomplish the desired result. If the agency which will handle this immense national material is merely an uncritical indexing agency, that effort will necessarily go to waste. There must be a sorting of the material that comes in by a competent critical agency before it is turned over to the indexing agency.

Components of this pool from various sources will be based on studies of varying competency, and differing durations of observation after the occurrence of the toxemia. Therefore, as these studies come in from individual clinics, they should be evaluated before being drawn into a pool from which broad deductions are to be attempted.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I believe that the most noteworthy point brought out in Dr. Kellogg's paper is the need of some central body to do what Dr. Cosgrove has suggested, and I think the most available source for the development of such a body is one of the national societies interested in this particular field. Without intending this to be derogatory, I doubt whether a Government agency which is interested in the statistical side of this question would be the one to undertake this study. An organization such as this Association could well take upon itself the duty of doing exactly what has been suggested. We have had a number of people who have tried to do this, but we are not getting anywhere

rine stimulated the uterus under these conditions. In 1927 Rucker,⁴ working on the hypothesis of the relation of the sympathetic system to uterine contractions, reported a relaxation effect of epinephrine on the contraction rings in dystocia. His records are in part graphic, but for the most part are clinical interpretations. Since that time a considerable number of observations have been made by many authors with conflicting opinions, some feeling that epinephrine is motor to the human uterus^{6, 8, 10, 14} and others that it is inhibitory.^{6, 7, 9, 13, 15-17}

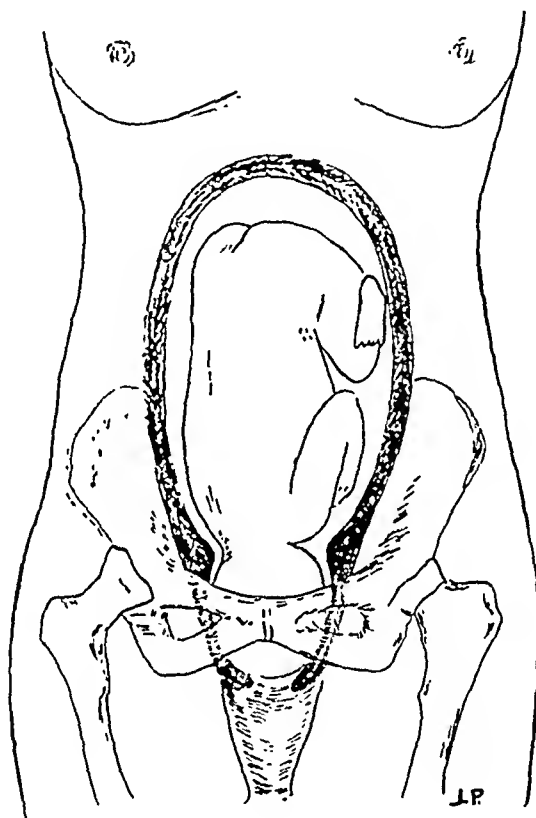


Fig. 1.—Diagrammatic drawing of contraction ring.

Clinically, epinephrine *alone* has seldom seemed satisfactory for the relaxation of these contraction rings. Because of the unsatisfactory clinical results from the use of epinephrine, and the great differences of opinion regarding its effect, it seemed wise to restudy this subject and try to obtain information on the human uterus.

Methods

During the course of our studies on uterine motility, we attempted to assay the effect of the administration of epinephrine on the laboring and post-partum uterus. While epinephrine was given both intravenously and intramuscularly, it was usually given intravenously in order that we might more easily record the beginning and end of the response obtained. Epinephrine solution 1:1000 was given in saline in

THE RESPONSE OF THE HUMAN UTERUS TO EPINEPHRINE*

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LABORATORY observations have frequently been transferred directly to clinical practice without the necessary critical study to determine their value or safety. Such superficial observations are frequent in medical literature and, once a positive statement has been made, it is copied repeatedly without recheck so that it is not long before this poorly established concept becomes a quoted dictum of therapy. Once these concepts have been made a printed record, they assume authority all out of proportion to their value, and the reader fails to critically analyze the evidence which led to that conclusion. It then requires a large accumulation of negative information to compensate for this one positive statement. This seems to be true of the recommended use of epinephrine in treatment of tetanic cervix and hourglass contractions of the uterus.

Because of confusion involved in terminology, throughout this report we shall use the term "contraction rings" to include all of those variants of uterine contraction known as Bandl's ring, retraction rings, hourglass contractions, and others. While it is possible that these may represent different clinical entities, we are inclined to agree with Rudolph,¹ who describes these as an exaggeration of the normal process of uterine contraction and retraction, and that these pathologic states represent an accentuation to an abnormal degree of physiologic processes.

A contraction ring may be defined as a localized area of tetanic uterine contraction which interferes with the process of labor (Fig. 1). The best evidence seems to suggest that this is a disturbance in uterine activity resulting from abnormalities within the uterus itself. Whether there is a disturbance in the neurogenic reflex arcs of the sympathetic system is still unknown. While many factors (pituitrin, intrauterine manipulation, forceps, etc.) may precipitate this process, contraction rings develop most frequently as a complication of fatigue, dehydration, and prolonged labor.

One of the earliest reported studies of the action of epinephrine on the uterus was made in 1912 by Dale and Laidlaw,² using the isolated intact uterus, and uterine strips of the cat and guinea pig. These observers noted that the spontaneous contractions of the uterus were abolished by the addition of epinephrine. In 1913 Gunn³ studied the isolated human uterus (both intact and muscle strips) and reported that epineph-

*Read at a meeting of the American Federation for Clinical Research, Minneapolis, 1942.

The duration of the effect of epinephrine on the human uterus varied somewhat but in general lasted less than four minutes or until the next independent contraction. This effect is manifested by a zone of inactivity which compares in type to the pause which follows extrasystole in the cardiac. There was no drop in the uterine base line, so

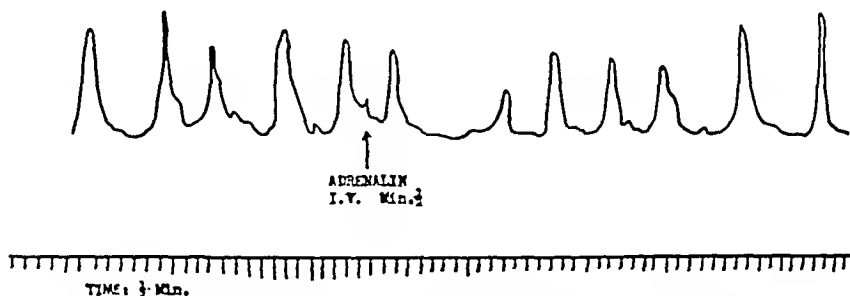


Fig. 3.—Laboring uterus; epinephrine injected intravenously.

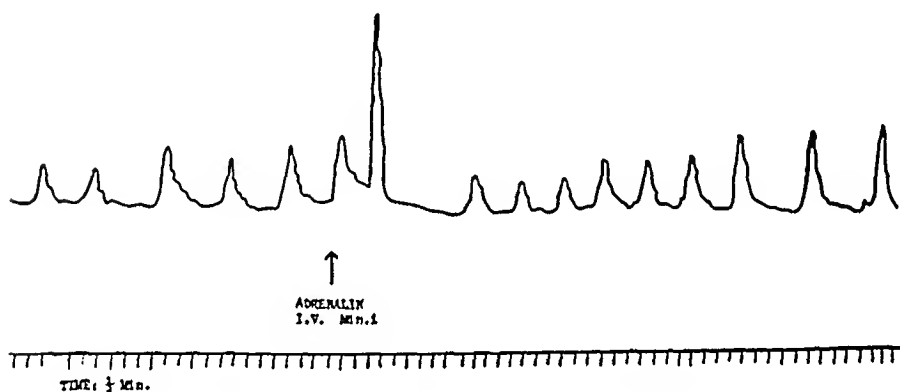


Fig. 4.—Laboring uterus; epinephrine injected intravenously.



Fig. 5.—Laboring uterus; epinephrine injected intramuscularly.

that we believe this represents a disturbance in rhythm rather than an alteration in uterine tone. We are unable to demonstrate the increased tone recorded by Woodbury⁵ or Gunn.³ Throughout these observations no evidence was adduced to support the theory that the cervix relaxes under the influence of epinephrine. Had the cervix relaxed the hydrostatic bag would have been expelled by the uterine contractions and this was not observed. The serial-recording observations of Ivy (Fig. 7) indicate that at least for the monkey, the cervix and body of the uterus react in the same manner, i.e., by contraction.

one to two minim amounts; while this is quite small it approximates that used in clinical practice.

The observations on the post-partum uterus were made on patients who were entirely normal and were between the fourth and eighth post-partum day. Under sterile conditions a Hegner bag was inserted in the uterus and connected by water to a mercury manometer and kymograph so that graphic records were obtained (Fig. 2).

The observations on the laboring uterus were made by similar direct manometric methods. On several occasions we were privileged to connect a Voorhees' bag, being used for the control of hemorrhage in placenta previa to a recording kymograph.

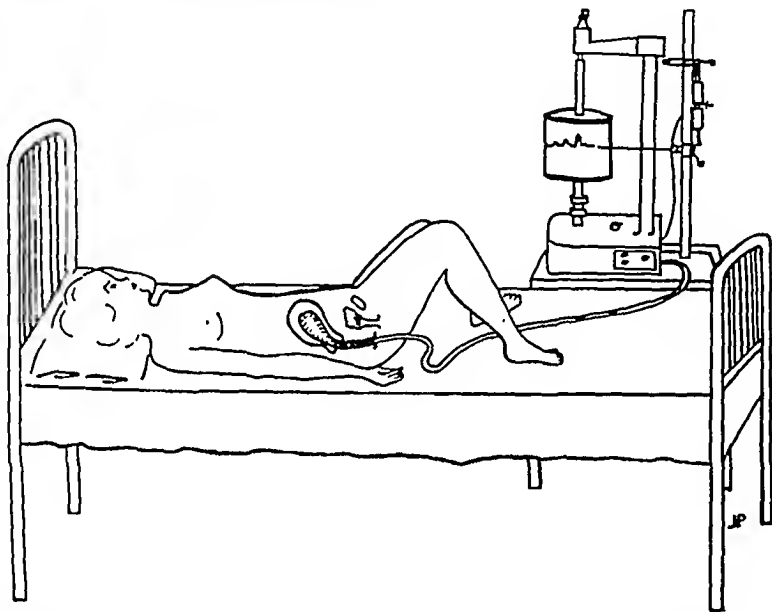


Fig. 2.—Method of obtaining curves. Hydrostatic bag was inserted into the uterus with antiseptic precautions. Contractions were recorded by a water-mercury float manometer.

Following the introduction of the bag a period of adjustment was permitted which varied from thirty to ninety minutes. The effect of epinephrine was studied on two types of uteri, laboring and puerperal. Some of the puerperal uteri exhibited spontaneous rhythmic contractions and in others the contractions were induced by an oxytocic (pituiric or ergot).

Results

The human uterus responds to intravenously injected epinephrine quite consistently by contraction, typical examples of which are to be found in Figs. 3 through 8. These induced contractions varied in magnitude but in general they represented an extrasystole type of response. This appears as an induced contraction which occurs prematurely in the cycle and is followed by a compensatory pause. If the uterus was contracting at the time of injection a greatly heightened contraction occurred (Figs. 4, 6, 8). No difference in response was observed between the spontaneously contracting uterus and the uterus with an oxytocically induced rhythm (Figs. 6 and 7). In no circumstances was there a drop in tone indicating a relaxation.

tain species (Table I, Group II) vary with the status of the uterus. We recognize that the normal laboring uterus and the puerperal uterus may not respond in the same manner as an abnormally contracting uterus showing contraction ring.

TABLE I. UTERINE RESPONSE TO EPINEPHRINE OF VARIOUS LABORATORY ANIMALS
(REVISED FROM REYNOLDS¹¹)

	ANIMAL	GRAVID	NONGRAVID
I.	Guinea pig Rat Mouse	Inhibitor	Inhibitor
II.	Cat Dog	Motor	Inhibitor
III.	Rabbit Squirrel Ferret Hedgehog Monkey	Motor	Motor
	Human	Motor	Motor

That epinephrine alone seldom adequately relaxes these contraction rings, has been the clinical experience of many obstetricians. Most authors^{13, 15-19} recommend the combined use of epinephrine and a general anesthetic. If one recalls that intramuscularly injected epinephrine does not become effective for several minutes, it is more likely that the relaxation produced under this schedule is the result of the anesthetic. It is our own impression from clinical observations that no advantage is obtained from the use of epinephrine in contraction rings. This opinion is based on both abdominal palpation and vaginal examination of the patients treated with epinephrine.

If epinephrine were simply valueless in the management of contraction rings, our observations would be of academic interest only. However, in a fatigued, dehydrated and shocked patient who is in the excitement phase of ether anesthesia, epinephrine carries a serious potential risk which we are not warranted in inflicting on our patient unless we can demonstrate clear-cut and unquestioned value. Under such conditions epinephrine may very well further contribute to the development of shock by increasing the spasm of already constricted arterioles, and thus continue the vicious cycle of capillary stasis, tissue anoxia, and eventual circulatory collapse.²⁰ Epinephrine also increases the irritability of an already rapid heart,²¹ further accelerating it to the point of diminishing volume output, and may initiate a disturbance of rhythm such as ventricular premature systole.

Since we are unable to demonstrate any value from epinephrine, and because the dangers which may result from its use are greatly increased in the obstetric conditions developing in contraction ring dystocia, we believe it unwise to use epinephrine in the management of this complication.

These findings are in accord with the observations of Woodbury and others;⁵ Ivy and others;⁶ and Bourne and Burn as far as rhythm changes are concerned. Ivy,⁶ and Bourne⁷ have recorded the same type of curves obtained in our studies. Thus the confusion that has existed

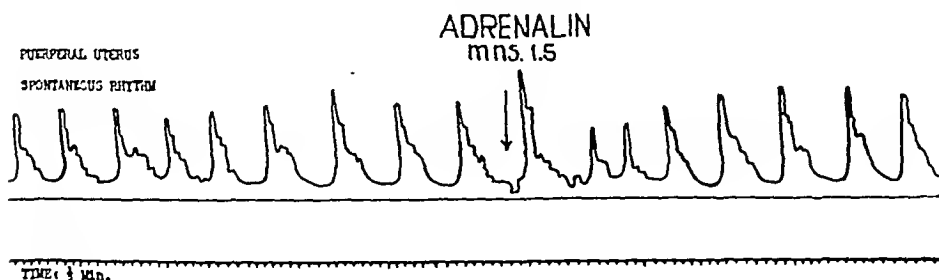


Fig. 6.—Puerperal uterus, spontaneous rhythm; epinephrine injected intravenously.

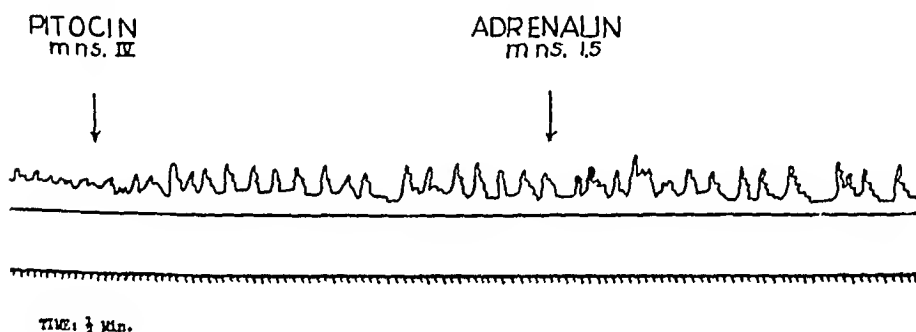


Fig. 7.—Puerperal uterus, pitocin induced rhythm; epinephrine injected intravenously.

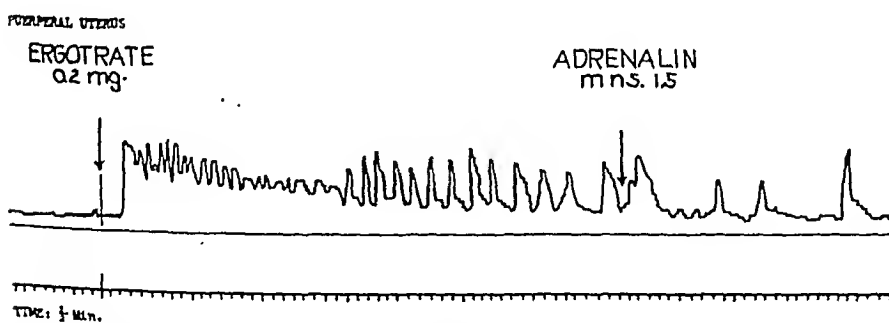


Fig. 8.—Puerperal uterus, ergotrate induced rhythm; epinephrine injected intravenously.

regarding the response of the human uterus to epinephrine resolves itself into an interpretation of what constitutes inhibition. The apparent inhibition claimed by one group, we believe, is the refractory state of muscular activity rather than a drug effect.

From our own observations and a more critical interpretation of the curves published in the literature we believe that epinephrine stimulates the human laboring and puerperal uterus to contraction. Table I, modified from Reynolds,¹¹ explains some of the differences of opinion in the literature. Animals vary in their response to epinephrine, and in cer-

PERIPHERAL BLOOD FLOW DURING GESTATION*

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IT IS generally accepted that the pregnant state is associated with cardiovascular changes of considerable magnitude. Obviously, since the growing embryo requires additional nourishment, and since the waste products consequent to its metabolism must be excreted, a gradually increasing burden is placed upon the maternal circulation. In 1915, Lindhart¹ found that the cardiac output in the one pregnant patient studied increased 50 per cent during gestation. This result has subsequently been confirmed by a number of investigators.²⁻⁵ Associated with the augmented cardiac output is a definite elevation in pulse rate which tends to increase gradually until term and then falls immediately after delivery. The changes in blood pressure are not significant nor constant, although there is a tendency for a widening of the pulse pressure during the fourth to the ninth lunar months.

Besides the above changes, a number of workers^{6, 7} have reported a progressive increase in plasma and total blood volume, which, according to Cohen and Thomson,⁸ may well be the cause for the augmented cardiac output. The latter investigators have also confirmed the observation of Pelissier⁹ that the viscosity of the blood is decreased during at least the first nine lunar months of pregnancy.

With such definite alterations in the dynamics of the circulation, it would be expected that the blood flow to the extremities is likewise affected. In this respect, Huchart¹⁰ postulated the existence of peripheral vasoconstriction in pregnancy and for many years this idea was generally accepted. In fact, it has been considered that a circulating vasopressor substance is the responsible agent, although no definite evidence to support such a point of view has ever been presented. The velocity of the blood in pregnancy has been extensively studied,¹¹ most of the reported readings falling within the range of normal, nonpregnant women. However, according to Cohen and Thomson,^{11a} there is a trend toward an increase up to the thirty-sixth week.

In the present investigation, the actual rate of resting peripheral blood flow was determined in a series of pregnant women, using the venous occlusion plethysmographic method.

Method

Blood flow readings were made at monthly intervals or at less during the last two trimesters of gestation and for a month or two after de-

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Conclusion

1. The human uterus can serve as a useful means of studying the action of certain drugs which have been studied on experimental animals: It is only by this means that we may avoid the pitfalls of directly transferring animal studies to the human being.
2. The action of adrenalin was studied on three types of human uteri: (a) laboring uteri with spontaneous rhythm, (b) puerperal uteri exhibiting spontaneous rhythm, and (c) puerperal uteri with an oxytocically induced rhythm.
3. Epinephrine causes a premature contraction of the uterus which is followed by a short latent period (compensatory pause) but without evidence of relaxation.
4. Any apparent relaxation which follows epinephrine is always preceded by a period of increased activity.
5. We find no evidence to support the use of epinephrine in disturbances of uterine contraction such as Bandl's ring, retraction rings, etc.
6. Because of fatigue, dehydration, and shock, epinephrine is potentially dangerous in these patients and is not recommended.

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the range of the determinations obtained in the control series (an average for the whole group of 1.6 c.c. per minute per 100 c.c. limb volume, as compared with 1.3 c.c. for the nonpregnant women). Fig. 1 is typical of the circulatory changes in the leg observed during the period of gestation. In 1 of the subjects (L. C.) there were some variations in the individual figures, but these were no more marked than those noted in the group of nonpregnant women taken at intervals over the same period of time.

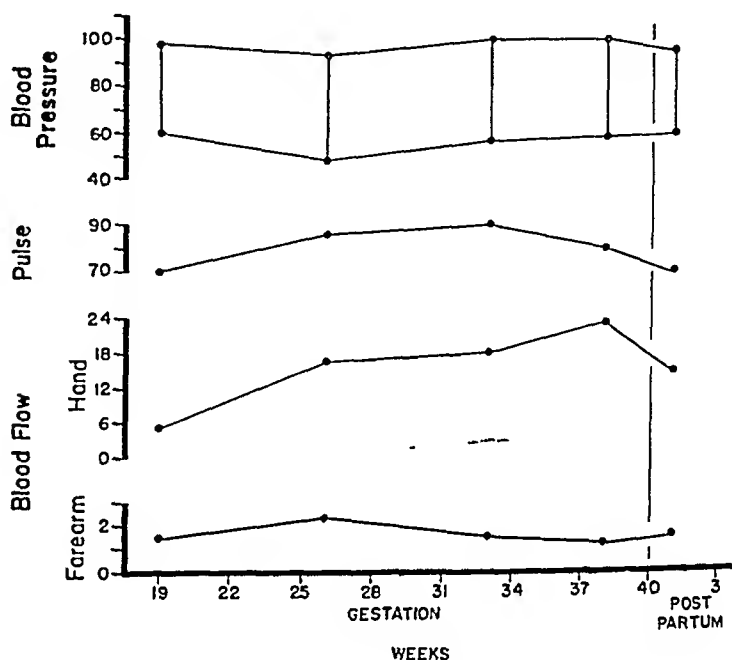


Fig. 2.—Blood flow changes in hand and forearm in Subject I.G. Readings in cubic centimeters per minute per 100 c.c. limb volume. Definite increase in blood flow observed during period of gestation, with a tendency toward a fall after delivery.

The forearm was examined in 11 subjects, and in 8 of these the readings obtained during the period of gestation again fell within the range for normal determinations (an average of 1.6 c.c. for the group, as compared with 1.5 c.c. for the normal series) (Table II). Typical responses

TABLE II. RESTING BLOOD FLOW IN FOREARM DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
F. F.					1.8	1.3	1.2	1.4			
L. L.					1.8		1.6		1.2		1.9
B. S.				1.4		1.9				2.4	
R. S.		2.2		2.0	1.7	2.0				1.9	
L. C.		1.7				1.5		1.3	1.5		
I. G.	1.5		2.3						1.0		
L. F.	1.5		2.4	1.7			1.9				1.9
C. S.							1.6	1.1			
A. G.		3.6	2.3	2.7		1.8		1.5			
H. F.			2.3	3.2					1.5		
L. A.				2.0		2.2	2.4	3.6	3.1	2.5	2.6

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

livery. Twelve normal pregnant women and one with fully compensated mitral stenosis were utilized in the study. The rate of blood flow was determined separately in the hand, forearm and leg at a bath temperature of 32° C. (temperature of the water in the plethysmograph) and at a room temperature of 25° to 27° C., according to the technique previously described.¹² The blood pressure and pulse rate were recorded on each occasion.

Results

For comparison with the data obtained in the pregnant subjects, a series of 45 normal, nonpregnant women of approximately the same age group was used. The blood flow in the leg was found to be 1.3 c.c. per minute per 100 c.c. limb volume (σ -0.4),* in the forearm, 1.5 c.c. (σ -0.5) and in the hand, 7.2 c.c. (σ -3.1).

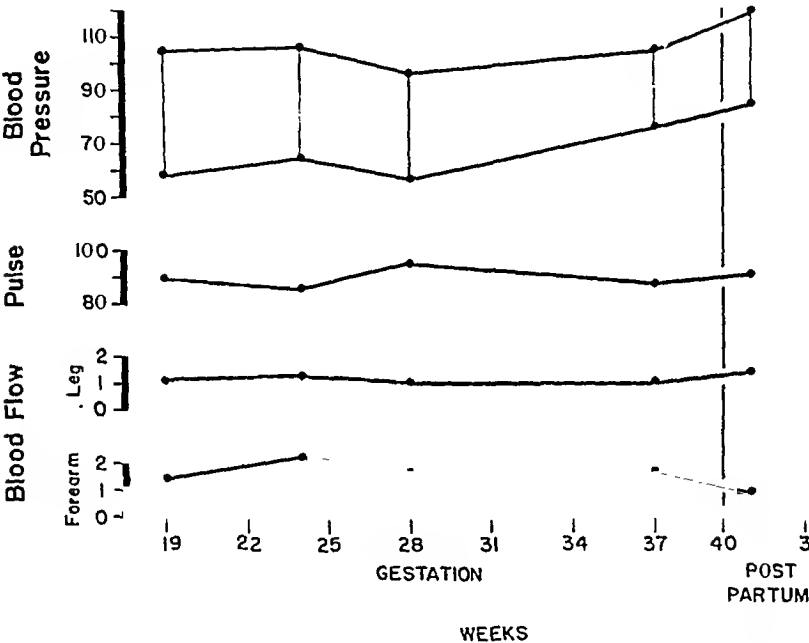


Fig. 1.—Blood flow changes in leg and forearm in Subject L.F. Readings in cubic centimeters per minutes per 100 c.c. limb volume.

Blood Flow During Gestation.—The leg was examined in 5 subjects, in each case on the average of 3 to 4 times during the period of pregnancy (Table I). In every instance the blood flow readings fell within

TABLE I. RESTING BLOOD FLOW IN THE LEG DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
F. F.											
L. L.											
L. A.											
L. C.			2.0	1.8	2.1	1.7	1.6	2.1			
L. F.	1.2	1.8	1.4	1.2	1.1	1.1	1.2		1.5	2.2	

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

*Standard deviation.

a slight decrease in pulse pressure as a result of a similar alteration in the systolic blood pressure level, the diastolic pressure for the most part remaining unchanged. With respect to the pulse rate, the readings were generally higher than normal, with a tendency toward a fall either in the last months of pregnancy or in the post-partum period (Figs. 1 and 2).

Discussion

From the foregoing, it is clear that the changes in the local circulation through the forearm and leg in gestation are for the most part negligible, despite significant alterations in the general hemodynamics. Certainly the hypothesis that there is a vasoconstriction of the blood vessels in the extremities in this state is not supported by our findings. In view of the increased cardiac output, one might theoretically have expected an augmentation of peripheral blood flow, but, with the exception of 3 cases, this was not apparent in the forearm or leg. Evidently, then, the increased quantity of blood ejected by the heart is utilized in the main in satisfying the greater requirements of the uterine circulation; little, if any, selective shunting of blood from the extremities to the placenta taking place.

It is of interest to note that despite the consistent finding of an elevated venous pressure in the lower extremities in pregnancy, in consequence of the increased resistance to venous return by the enlarging uterus,^{5, 13} the rate of blood flow in the leg remains normal. This is further proof for the view that changes in the venous side of the circulation, unless marked, do not necessarily affect arterial inflow.

The results in the hand merit further discussion. It appears quite probable, on the basis of our data, that there is a definite trend toward an increase in the rate of blood flow through this vascular bed as the pregnancy progresses. Since the hand ordinarily plays an important role in body heat conservation and dissipation, it was at first considered that the altered maternal circulation through this site was a manifestation of the mechanism whereby the heat produced by the metabolic processes in the fetus is removed. However, the fact that in a number of subjects the rate of blood flow in the hand did not diminish in the period immediately following parturition would be opposed to this view. Another explanation may be related to the observation that in pregnancy there is an increase in oxygen consumption, which is greater than that expected on the basis of the sum of the high metabolic rate of the fetus and the augmented maternal respiratory work.¹⁴ It is possible, therefore, that an overfunction of the thyroid gland¹⁴ might be the explanation for the high blood flow in the hand. It is of interest that all of the women in the series volunteered the information that, except for the first few months, their hands and feet had become very much warmer during gestation. In 9 of these cases the extremities were ordinarily quite cold. Since all of our studies were made during the

are noted in Figs. 1 and 2. It is of interest that in the patient with compensated mitral disease (L. C., Table II) the results in the forearm and leg were similar in all respects to those already described for normal subjects.

In the remaining 3 of the 11 subjects in whom the forearm was studied, a number of the determinations obtained during the period of gestation were definitely increased (an average for all of the determinations of 2.5 c.c. as compared with 1.5 c.e. [σ -0.5]) for the nonpregnant women. No consistent trend, however, could be noted. In one instance (A. G.) the readings were initially high, to decrease as term was approached, while in another (L. A.) the reverse was true. In the case of H. F., the results were indefinite, since only two determinations could be obtained before the subject went into premature labor at the end of the thirty-eighth week of pregnancy. These patients differed in no way from the others in the group in respect to blood pressure or pulse rate changes.

The hand was repeatedly examined in 7 subjects (Table III) and in all instances a significant increase in the rate of blood flow was noted as the pregnancy advanced. This is clearly demonstrated when the average control figure of 7.2 c.e. per minute per 100 c.c. limb volume (σ -3.1) is compared with the readings obtained in the last two trimesters of gestation (Table III). Fig. 2 is typical of the increase in hand blood flow observed during the pregnant state.

TABLE III. RESTING BLOOD FLOW IN THE HAND DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
B. S.							11.7		8.3		4.2
L. A.							21.3	15.8	26.3	9.7	14.0
I. G.	5.1		16.8			18.0		23.8	14.2		
A. G.		10.0		14.3		16.8		18.2			
C. S.							9.1	10.6			10.4
R. S.		5.4		12.4		25.4				7.7	
H. F.		9.8		15.6					23.2		

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

Blood Flow in the Post-Partum Period.—It was not possible to obtain readings on all of our subjects following delivery, but sufficient data were accumulated to warrant drawing certain conclusions. In all instances in which the rate of blood flow in the forearm and leg remained within the normal range during the pregnant state, no significant change occurred in the post-partum period (Tables I to III, Figs. 1 and 2). In the case of the three subjects in whom an increased forearm blood flow had been noted during gestation, normal readings were observed after delivery. In respect to the hand, the fall in blood flow was not always observed immediately, the figures remaining elevated in a number of the cases for some time afterwards. The first set of results obtained in the post-partum period for L. A. and H. F. cannot be considered to be uncomplicated readings, since the tests were performed at the time of onset of lactation.

Blood Pressure and Pulse Rate Changes During and After Gestation.—The blood pressure readings in the series did not vary significantly during the period of pregnancy (Figs. 1 and 2). In 3 instances there was

THE PROBLEM OF ABORTION*

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THAT the problem of abortion is one of progressively increasing importance is evidenced by the fact that its incidence has increased by an appalling percentage during the last several decades. This is particularly true of induced abortion. Taussig,¹ in his book on the subject, estimates that the ratio between abortions and confinements is 1:2.5. In itself this would not be alarming were it not for the fact that the mortality rate in a most conservative estimate is 1.2 per cent throughout the country. Interpreted statistically, of the estimated 680,000 abortions in the United States in 1941, at least 8,200 terminated fatally. This is a figure which approximates the maternal mortality associated with term-confinements. The relatively recent increase in the prevalence of abortion is attributable in large part to certain social factors: The dishonorable stigma accompanying illegitimacy, the attempt to escape the responsibilities of parenthood, the poverty and squalor attendant upon the depression of the last ten years, the desire to raise the economic level of living by restricting the size of families, by methods most reckless and foolhardy if need be, the migration to the attractions of the cities, and in general the desertion of idealism in favor of a more secularized philosophy, especially manifest since World War I, are all contributory factors. It is the momentous significance of the problem that suggested this study by several of us at the Milwaukee County Hospital.

Material

Herewith are reviewed 800 consecutive abortions, a series which includes all the abortions of every type treated in this Hospital during the years 1937, 1938, 1939, 1940, and the first three months of 1941. To avoid confusion, a brief review of the definition of terms accepted on our service is included.

In its most exacting definition, abortion includes all cases where detachment or expulsion of the fertilized ovum occurs before viability,¹ i.e., twenty-six to twenty-eight weeks. However, for the sake of convenience, this series includes only those cases where pregnancy was terminated before the fifth month; pregnancies beyond this period are treated on the obstetric rather than on the gynecologic service. This differentiation is made since Wisconsin state laws require neither a birth certificate nor a death certificate unless the gestation has proceeded beyond five months or twenty weeks.

*Presented at a meeting of the Wisconsin Society of Obstetrics and Gynecology, May 15, 1942.

winter months, the high blood flow in the hand is of significance, for under such circumstances it could not have been due to the external temperature.

Summary and Conclusions

The resting peripheral circulation was investigated in 13 women, first in the pregnant state and then during the post-partum period. By means of the venous occlusion plethysmographic method, the rates of blood flow in the hand, forearm and leg were studied separately.

It was found that in the majority of the cases the blood flow in the leg and forearm remained within normal limits during at least the last two trimesters of gestation, while in the hand there was a definite trend toward an increase in circulation. In no instance was a decrease in the rate of blood flow observed in either the forearm, leg or hand.

It is concluded that the increased uterine circulation during gestation is obtained primarily through the mechanism of an augmented cardiac output and not at all at the expense of the blood flow to the extremities.

Valuable technical assistance was contributed by Mrs. W. Littleford.

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on the incidence of spontaneous abortion. Judging from our figures, one would be inclined to believe that the white race is less susceptible to spontaneous abortion than is the Negro race, since 43 of this group were colored, a figure not in proportion to the Negro census in this Hospital. Syphilis is no longer considered an important etiologic factor responsible for early spontaneous abortion; in fact, only 14 women in this large group had positive Wassermann reactions. Occasionally one hears the remark that first pregnancies are more likely to terminate in spontaneous abortion than are subsequent gestations. This statement is not confirmed by our data, since the incidence is practically the same in women who are pregnant for the first, second, third, or fourth time. The sharp decline in the occurrence beyond this number of gravidity can be explained by the fact that relatively few women have more than four children.

TABLE III. COMPARATIVE INCIDENCE OF ABORTION IN RELATION TO AGE

TYPE	AGE							TOTAL
	15-20	20-25	25-30	30-35	35-40	40-45	45-50	
Spontaneous	43	139	148	104	75	41	3	553
Self-induced	7	32	37	25	17	4	1	123
Criminally induced	3	9	10	1	4	--	--	27

For the most part, all age groups are affected in a ratio directly proportional to the fertility age of women.

TABLE IV. COMPARATIVE INCIDENCE OF ABORTION IN RELATION TO GRAVIDITY

TYPE	GRAVIDITY								TOTAL
	I	II	III	IV	V	VI	VII	VIII AND UP	
Spontaneous	75	90	86	78	47	47	41	89	553
Self-induced	17	17	26	20	10	16	3	14	123
Criminally induced	11	5	2	5	3	--	--	1	27

TABLE V.

TERM OF GESTATION	NO.
One month pregnant	75
Two months pregnant	207
Three months pregnant	161
Four months pregnant	110
Missed abortion	6

The highest incidence of spontaneous abortion occurs in the second month of gestation. An interesting observation was the high incidence of previous pelvic surgery in the women who experienced spontaneous abortions. Seventy-one women in this group had already been subjected to surgery of one type or another on their internal generative organs.

Among the more serious medical complications with which this group of women was afflicted are those given in Table VI.

In only 125, or less than one-fourth, was there evidence that all the products of conception definitely had been expelled or delivered either prior to admission or on entry into the hospital so that a diagnosis of complete abortion was justifiable.

In noninfected spontaneous abortions, severe anemia is not common. A leucocyte count above 15,000 is the exception and a sedimentation

In threatened abortion, which is characterized by uterine contractions and a bloody show, the ovisac itself has not yet been detached. Incomplete abortion is the more advanced stage, in which portions of the products of conception are expelled and the remainder are retained within the uterus. On the other hand, in complete abortion all the gestational products have been expelled. Spontaneous abortion is one initiated by intrinsic causes, in contrast to induced abortion, in which external factors are responsible. The induced or illegal abortion as it is sometimes termed, may have been perpetrated either by the patient herself, the so-called self-induced abortion, or by a second party, the so-called criminally-induced abortion. In a missed abortion, the pregnancy is retained intact for longer than two months after the death of the fetus.

We have subdivided all abortions further into febrile and afebrile groups, arbitrarily defining the febrile or septic patient as one in whom the temperature has risen to 100.4° F. on any two hospital days excepting the day of admission. The exclusion of the day-of-admission temperature is made because of the inexplicable occurrence of a low-grade fever in a large percentage of patients at the time of their entry into the hospital which subsides without treatment or recurrence shortly thereafter.

TABLE I. INCIDENCE

1937	182
1938	296
1939	150
1940	141
1941 (first four months)	31
Total	800

Table I shows the comparative incidence of abortions in the last four years. We cannot account for the increased incidence in 1938.

TABLE II. COMPARATIVE INCIDENCE

Spontaneous abortion	553
(Including 76 which were admitted as threatened but went through the inevitable stage to completion, and including 6 hydatid moles)	
Self-induced abortion	123
Threatened abortion, treatment successful	91
Criminally-induced abortion	27
Missed abortion	6
Total	800

Spontaneous

Of the 553 spontaneous abortions, only 53, or 10 per cent, were febrile; whereas 57, or approximately 50 per cent, of the 123 self-induced abortions were febrile, and 11, or roughly 40 per cent, of the 27 criminal abortions were septic. In other words, the incidence of infection is four to five times as great if the pregnancy has been tampered with by outside interference. Our statistics show further that age is not a factor in the incidence of spontaneous abortions, since all age groups were represented in a ratio directly proportional to the fertility age of women. As one would expect, social status or religious affiliation has no effect

in itself absolutely necessitates the procedure, invasion of the infected uterus is considered unjustified.

Of the 553 spontaneous abortions, 481 patients received one or more courses of oxytocics; in 181 cases, a pack was inserted; only 27 of the women required one or more transfusions; and in only 120 cases, or approximately one-fifth of the total, was dilatation and curettage performed because evidence existed demonstrating that the uterus (after a conservative period of three or more days) still contained some fetal or placental elements.

The average hospital stay for the patients so treated was 7.6 days, the shortest one day, the longest thirty-nine days. Thirteen patients were curetted immediately on admission to the hospital; their average stay was 9.4 days. The treatment of the 53 infected spontaneous abortions consisted essentially of oxytocics, repeated transfusions of whole blood, and sulfanilamide or its derivatives since it became available on our service in 1938. Eight of these patients were curetted only after a reasonable period of normal temperatures permitted. The average hospital stay for the septic spontaneous abortions was 15.8 days; the average number of days morbidity was 4.8. There were no deaths in the entire series of spontaneous abortions.

Threatened Abortion

Here treatment has been quite discouraging. Of the 167 cases that were diagnosed as threatened abortion on admission, only 91 were discharged with the pregnancy supposedly salvaged. The remaining 76 continued on through the inevitable stage into either an incomplete or complete abortion. We do not attempt to excuse these unfavorable results by explaining that in many instances the patient had so long neglected her symptoms of bleeding and pain that when she finally sought medical attention in the hospital, the abortion should have been classified on admission as inevitable rather than threatened. Having made use of all of the suggested medications, beginning with the opiates, through the barbiturates, atropine, thyroid extract, wheat germ oil, corpus luteum, up to the most recently advocated progesterone, our results would seem to indicate that if a blighted ovum of defective germ-plasm is growing, nature will empty the uterus regardless of any measures which might temporarily inhibit uterine contractions. However, since one cannot determine objectively in which cases a healthy trophoblast is developing, all measures possible should be instituted to maintain the uterus in a state of quiescence until the disturbing factor is eradicated. Our statistics indicate that treatment of threatened abortion is more successful if the gestation has advanced beyond the first month, since we were able to save only three cases in which the patient had missed but one menstrual period and the Friedman test had verified the diagnosis of pregnancy. The fact that in every threatened abortion that we were able to save, the erythrocyte count was above three million, would tend to substantiate the contention that severe anemias predispose to abortion. Furthermore, we are satisfied in our own minds that a uterus once infected cannot and will not retain the pregnancy, for in not a single instance were we able successfully to prevent an infected uterus from emptying its contents.

TABLE VI. COMPLICATIONS

Rheumatic heart disease	8
Hyperthyroidism	8
Pulmonary tuberculosis	7
Chronic nephritis	7
Diabetes mellitus	3
Hypothyroidism	2
Thyrotoxic heart disease (decomp.)	1
Congenital heart disease (decomp.)	1
Hypertensive heart disease (decomp.)	1
Acute agranulocytosis	1
Scarlet fever	1
Carcinoma of breast	1
Carcinoma of cervix	1

rate above 100 mm. precipitation (Westergren) is a rarity. For that matter, there was surprisingly little difference between the laboratory findings in the infected and those in the noninfected spontaneous abortions.

The key to our treatment of abortion revolves around the word "conservatism." This is made possible by the fact that in a charity institution cost of care is not a pressing problem. It is admitted, however, that in private practice, where the patient is paying for each hour's stay in the hospital, such conservatism is not entirely feasible, and that immediate evacuation of the uterus upon making a diagnosis of inevitable or incomplete abortion in the absence of sepsis, may expedite recovery in selected cases.

The method of management of our cases is essentially as follows: Immediately upon admission, a careful sterile vaginal and speculum examination is made for the purpose of both diagnosis and treatment. Any tissue palpable or visible within the vaginal or cervical canals is removed with a sterile ovum forceps, the uterine cavity itself not being invaded.

Specimens of all tissue removed are examined by the pathologist. A microscopic study verifies the diagnosis, and his report has been found invaluable on many occasions as the only tangible evidence for medico-legal testimony. An oxytocic, either pituitrin or ergotrate, is then administered. If all the products of conception have been discharged from the uterus, bleeding will have ceased. If, on the other hand, any tissue remains, bleeding will continue. In the latter instance, a pack saturated with a 5 per cent aqueous solution of mercurochrome is inserted into the external os of the cervix and vagina. The pack is removed within twelve to twenty-four hours and not infrequently the remainder of the products of conception will be found then lying free and accessible. We hesitate about packing the infected uterus and strenuously emphasize against permitting a pack to remain more than six hours in the presence of fever. To hasten involution, a course of oxytocics, usually consisting of ergotrate gr. $\frac{1}{320}$ every four hours for six doses, each dose being accompanied by quinine sulfate gr. ii, is given. The patient is subjected to a dilatation and curettage only if, after three to five days, uterine bleeding is more profuse than a normal lochia. Except in those instances where hemorrhage is brisk and the bleeding

was used is small, we cannot accurately evaluate its merits. Without a doubt, the greatest share of credit belongs to the most efficacious therapeutic agent we have at our disposal, namely, transfusions of whole blood. Infections attributable to the anaerobic streptococcus are characterized by an anemia due in large part to the proteolytic action of the organism on erythrocytes and certain strains of this organism are notoriously resistant to chemotherapy. Whole blood, then, not only compensates for the blood loss due to the hemorrhage which characterizes neglected abortions, but also combats the anemia due to the bacterial hemolysis. Its polyvalent effect goes further, for not only is it beneficial as a supportive measure, as physiologic nourishment and to counteract dehydration, but its bactericidal effect is reflected by an immediate elevation of the phagocytic titer of the patient's blood. For the anemic, infected postabortal patient, the administration of repeated small transfusions, 250 to 500 c.c. of whole blood daily or on alternate days, is strenuously advocated.

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THE PROBLEM OF UNSUSPECTED TUBERCULOSIS DURING PREGNANCY IN THE NEGRO

Incidence by Roentgenologic Techniques in 1,000 Consecutive Cases

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EISELE and associates¹ have in this JOURNAL recently again called attention to the importance of the problem of the unsuspected cases of clinically important pulmonary tuberculosis among any series of prenatal patients. They have presented data on the examination of 10,968 pregnant white women by fluoroscopy and x-ray at the Chicago Lying-in Hospital. Examination demonstrated an incidence of 1.0 per cent clinically important tuberculosis as found by this method, to be contrasted with a discovered incidence less than one-tenth as great when no roentgenologic technique is employed for the detection of the disease.

Eisele and associates give figures for the incidence of tuberculosis in a white prenatal group, and in an institution exclusively for the care of obstetric and gynecologic problems, in a large metropolitan area. Various studies have shown that the incidence of tuberculosis will vary with the definition of the particular group investigated. It will therefore be of interest to compare with Eisele's figures the findings, accord-

Self-Induced Abortion

All kinds of devices were admittedly employed in this group of cases. The remarkable ability of the uterus to limit infection is evidenced by the fact that only 57 of the 123 self-induced abortions became septic. This entire series included but three negroes. Thirty-seven of this group became pregnant out of wedlock. Gravidity and parity play no part in this story. Only twelve had missed but one menstrual period; the remainder, apparently hoping the amenorrhea was due to some other factor, waited two or more months before they attempted interference. That the uterus is reluctant about relinquishing a healthy pregnancy is shown by the fact that only 18 of this entire series of 123 self-induced abortions were complete. Here, too, the management of these cases, either infected or not, was conservative. The average hospital stay for the afebrile group was eight days. In the infected group, the average number of days of morbidity was 6.5 and the average number of hospital days was 15.7. Three of these women with self-induced abortion died.

Criminal Abortions

As previously mentioned, there were 27 instances in which criminal induction was confessed. In all of these, an instrument was used. In 8, a physician was responsible; in 10, a midwife; and in the remainder, the accomplice was listed as "a friend." There were no colored women in this series. Sixteen, or more than half, were either single, divorced, or widowed, obvious instances in which the social stigmas of illegitimate pregnancy prompted their course. Strangely enough, only 4 had been emptied completely. Eleven of the criminal abortions were septic. There was one death in this group.

Summary and Conclusions

Although in this entire collection of 800 abortions, there were only four deaths, yet more noteworthy is the fact that not a single death occurred in the last 557 cases of the series. That an element of good fortune was present is admitted, although many of the women entered the hospital in critical condition due either to exsanguination or sepsis or a combination of both; none were in actual extremis. However, there are several points in the modern mode of treatment that deserve attention. The practice of conservatism has been emphasized sufficiently. The administration of oxytocics, by provoking contraction of a sluggish myometrium, serves a dual purpose. Not only are avenues for extension of bacterial invasion through the uterine wall closed, but, by stimulating expulsion of necrotic debris from within the uterine cavity, the nidus of the contaminating saprophytes is eliminated. The judicious use of sulfanilamide and more recently of sulfapyridine and sulfathiazole, particularly against the hemolytic streptococcus, is now clinically well established, and we are certain that they have been responsible agents for lowering the morbidity and mortality rate since their introduction into our therapeutic armamentarium in 1938. Because the number of cases in which scarlet fever convalescent serum

gestation complicates the problem of adequate care for the patient, as usually the diagnosis is made too late to carry out safely a therapeutic abortion where such a procedure is indicated. The distribution of the stage of gestation at the time of the first examination at Provident Hospital contrasted with that at Lying-in Hospital, is shown graphically in Fig. 1.

For reasons largely sociologic Negro women tend to become pregnant somewhat earlier than white women, and to continue bearing children longer. At Provident Hospital, including all multiparas with primiparas, the average age of prenatal patients was 24.2 years; at Chicago Lying-in Hospital the similar average reported by Eisele¹ was 25.8 years. The distribution of pregnant women by age groups in the two institutions is compared in Table II.

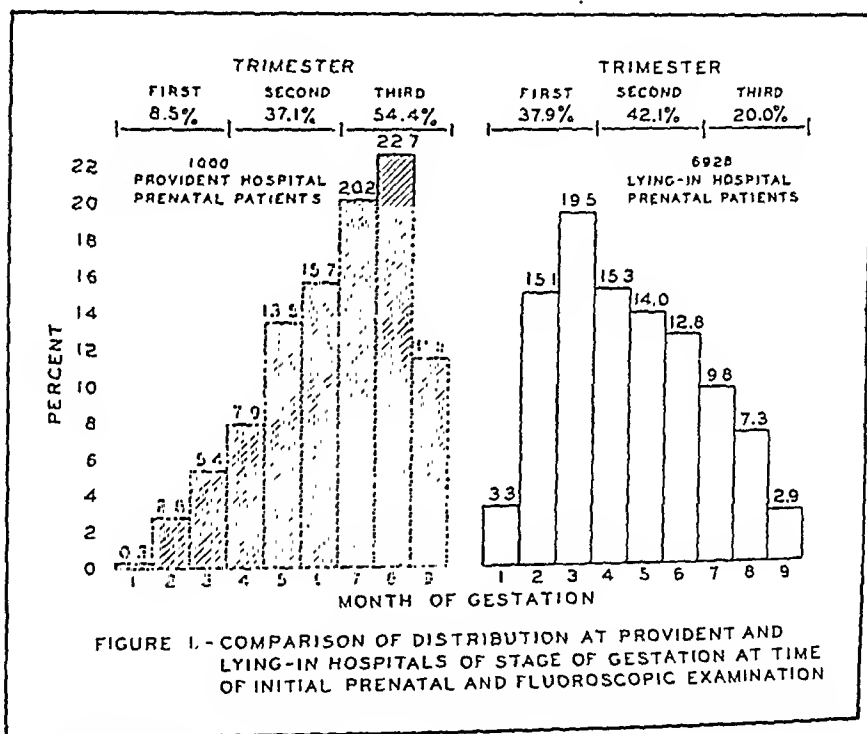


Fig. 1.—Comparison of distribution at Provident and Lying-in Hospitals of stage of gestation at time of initial prenatal and fluoroscopic examination.

Thus it is seen that the average Negro prenatal patient seen at Provident Hospital is slightly younger than the average prenatal patient at Lying-in Hospital, is seen at a somewhat later stage in gestation, and is of a somewhat lower economic group.

These differences may serve to account for the different incidence noted at Provident Hospital. Among the 1,000 consecutive prenatal patients examined over a thirty-month period, 18 cases of clinically im-

TABLE II

AGE GROUP	PER CENT IN AGE GROUP	
	LYING-IN HOSPITAL	PROVIDENT HOSPITAL
13-19	9.6	32.7
20-29	67.2	44.6
30 and over	23.2	22.7

ing to an identical method of examination, in a group of Negro prenatal patients, in the same city, at the Provident Hospital and Training School, an institution which gives general medical care to the large Negro population of Chicago.

Bloch and associates² have made a preliminary report on an investigation of the incidence of tuberculosis and other chest pathology among clinic patients of the Out-Patient Department of Provident Hospital, in a study begun in November, 1939. A fluoroscopic unit was installed as an integral part of the admitting routine of that Department, and all patients have had a chest fluoroscopy in addition to other routine laboratory investigations since that time. When definite or suspected lesions of clinical importance are seen on fluoroscopy, an x-ray of the chest is ordered, and it was their experience that about 7 per cent x-rays were ordered, about half of which showed definite pulmonary tuberculous pathology. The results to be presented here are those of the examinations of 1,000 consecutive patients attending the Pre-Natal Clinic of Provident Hospital, from November, 1939, to May, 1942, a group easily separated from the total number of out-patients so examined.

Material and Results

The patients attending the prenatal clinic are all of the Negro race. The vast majority are of the lower economic strata, and few are able to pay the full cost of their obstetric care. For the year 1941 of 131,379 visits to the Out-Patient Department of Provident Hospital only 5,323 (4.1 per cent) were pay visits, the remainder (95.9 per cent) free or relief agency cases. For 1940 the figures were practically identical. Approximately the same proportions apply to the women seen in the prenatal clinic. Provident Hospital is the only exclusively Negro hospital in Chicago to serve a population of approximately 300,000 Negroes. Most of the prenatal patients seen at Provident Hospital are cared for during the early months of their pregnancy at the dispensaries of the City of Chicago Health Department, and report to Provident for prenatal care and delivery only in the last trimester. This results in prenatal patients being seen at Provident later during gestation than in most prenatal clinics, the distribution at Provident contrasting with that at the Chicago Lying-in Hospital clinic, as reported by Eisele,¹ as shown in Table I.

TABLE I

GROUP	PER CENT EXAMINED IN		
	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Provident Hospital	8.5	37.1	54.4
Chicago Lying-in Hospital	37.9	42.1	20.0

The average woman reported to Provident Hospital for her initial prenatal examination and fluoroscopy when she was 6.42 months pregnant; the average woman at Lying-in Hospital was 4.53 months. As in the case of Eisele's figures for Lying-in Hospital, at Provident there was a slight tendency for those women found to have clinically important tuberculosis to report for their initial examination somewhat later than the average of the total group of prenatal patients. This inability to diagnoses clinically important tuberculosis sufficiently early during

incidence with increasing age, but a study of the incidence of all women in the total group studied at Provident Hospital³ does not indicate such a significant rise with age in women, although there is an increase with age in the men examined. The difference in age between the two prenatal groups, at Lying-in and Provident Hospitals, is slight. If Edwards is correct that there is not a significant difference on the basis of race, it would therefore appear that the noted difference in the incidence in the two institutions is probably on the basis of economic and other sociologic factors.

It is not the purpose of this report to discuss the relative merits of different methods of case-finding in tuberculosis. These have been amply stated by Eisele and associates,¹ who conclude that routine chest roentgenologic examinations are indispensable for detecting unsuspected tuberculosis in a prenatal population. The incidence of 1.8 per cent of clinically important pulmonary tuberculosis at Provident Hospital merely confirms and strengthens their contention that "tuberculosis in pregnant women is still an important problem, for although it has declined from first to seventh place as a cause of death in the general population, it still remains as the leading cause of death for women of the childbearing age." This is especially true in the case of Negro prenatal patients, for whereas the incidence of tuberculosis may not be greater in the Negro than in the white, the disease once of clinical importance tends to run a more unfavorable course in the Negro, and the mortality rate is from 3 to 4 times as high in the Negro as in the white, with a still higher ratio in the Northern states.⁵

It is not the intention of this report to offer a follow-up of the 18 cases of clinically important tuberculosis discovered by routine fluoroscopy and x-ray. A few case histories, however, will illustrate in a concrete fashion the problem of unsuspected pulmonary tuberculosis in a Negro pregnant woman, as it affects her health after delivery. Some of the more advanced cases, all with pulmonary tuberculosis not suspected prior to the initial fluoroscopic examination, have been selected for illustration, and demonstrate the seriousness of the problem. Other less extensive cases, all nevertheless active, naturally have had more favorable outcomes than these, but in every case the detection of the unsuspected pulmonary involvement has been a factor complicating the normal pre- and postnatal course.

CASE 1.—G. T., aged 18, gravida i, para 0, first visit to Prenatal Clinic Jan. 22, 1940, gestation $7\frac{1}{2}$ months. Fluoroscopy January 22 showed bilateral upper lobe tuberculosis. X-ray same day confirmed diagnosis of moderately advanced bilateral apical and subapical productive tuberculosis, with no evidence of cavitation. Only complaint that of a "cold" for three weeks; no history of tuberculosis contact in family or elsewhere. Four family contacts, mother and three sisters, fluoroscoped as contacts, all negative. Raising no sputum, none obtained for microscopic examination. Wassermann and Kahn, and urinalysis

portant tubereulosis were found, an incidence of 1.8 per cent, nearly twice the incidence at Lying-in Hospital; and 11 further cases of inactive, clinically unimportant tubereulosis, aside from calcifications of primary lesions, were discovered, a total of 29 cases, 2.9 per cent, of pulmonary tubereulosis of the reinfection type. Cases classified as clinically important included those definitely active with symptoms, and those without symptoms in whom the lesions did not demonstrate by x-ray sufficient evidence of healing by fibrosis and calcification. Cases classified as clinically unimportant were those in which such satisfactory evidence of healing by x-ray was present. In some cases observation of at least a year was necessary to classify the tuberculous lesion accurately. All 18 cases of clinically important tubereulosis were unsuspected, in the sense that they were not previously known to have such disease; and all were considered active, although most did not have symptoms when first seen. The incidence of reinfection tubereulosis by age groups is given in Table III.

TABLE III. INCIDENCE OF PULMONARY TUBERCULOSIS IN 1,000 PRENATAL NEGRO PATIENTS DISCOVERED BY ROUTINE FLUOROSCOPY, PROVIDENT HOSPITAL

AGE RANGE	TOTAL NO. IN AGE RANGE	CLINICALLY IMPORTANT TUBERCULOSIS		CLINICALLY IMPORTANT AND UNIMPORTANT TUBERCULOSIS	
		NO.	PER CENT	NO.	PER CENT
13-19	327	6	1.8	10	3.0
20-29	446	9	2.0	13	2.9
30 and over	227	3	1.3	6	2.6
Totals	1000	18	1.8	29	2.9

Average age 1,000 women at time of fluoroscopy, 24.2 years.

The study of the incidence of tubereulosis among prenatal patients at Provident Hospital affords an opportunity to compare it with the incidence of tubereulosis among other nonpregnant Negro women, of the same age groups drawn from the same general population, an opportunity not afforded by the study of Eisele and associates at the Lying-in Hospital. In women of the childbearing age the figures for the total group examined at Provident Hospital³ are: clinically important tubereulosis, 2.1 per cent, both clinically important and clinically unimportant tubereulosis, 3.2 per cent. The comparable figures for the prenatal group, 1.8 per cent and 2.9 per cent, respectively, are slightly but not significantly lower. It therefore would appear that prenatal patients at Provident Hospital have approximately the same incidence of tubereulosis as other women of the same age group coming to the same clinic.

Discussion

Edwards⁴ has presented figures which indicate that the lower the economic status of the group studied by x-rays, the higher in general the incidence of clinically important tubereulosis found. His figures do not indicate a significant difference in the incidence in Negroes and in whites. Others⁵ have reported the same experience. Edwards' figures, and those of Bloch and associates² indicate a slight increase in

months. No tuberculous contact history. Husband and two sons, fluoroscoped as contacts, negative. Physical examination showed breath sounds slightly decreased in right upper lung field; no râles. Sputum positive for tubercle bacilli twice, negative once, in February, 1941. Wassermann and Kahn, and urinalysis negative; blood counts normal. Was referred to and hospitalized in Municipal Tuberculosis Sanitarium on March 7, 1941; delivered there in July; artificial pneumothorax on right begun soon afterwards; discharged from sanatorium Jan. 16, 1942. Seen again in Chest Clinic, Provident Hospital, Feb. 24, 1942, symptom free; sputum negative. X-ray showed approximately 40 per cent collapse of right lung, left apical lesion doing well. Patient has since gained about 25 pounds in weight, is clinically doing well, is continuing to receive artificial pneumothorax therapy, 250 to 300 c.c. weekly.

CASE 4.—L. M., aged 20, gravida i, para 0, referred by Mery Free Dispensary to Provident Hospital, first seen at Provident in Prenatal Clinic on May 29, 1941; gestation nine months. Fluoroscopy and chest x-ray same day revealed moderately advanced exudative tuberculosis of the right upper lobe. Admitted to Provident Hospital afternoon of same day in labor, delivered normally that evening with episiotomy and usual repair. No chest symptoms, no tuberculous contact history. Mother fluoroscoped as contact, negative. Physical examination revealed slightly harshened breath sounds in right upper lung field; no râles. Left hospital, after normal post-partum course, on June 9, 1941. Sanatorium care advised but rejected. Seen in Chest Clinic at intervals from July to November, 1941, at first with no chest symptoms or altered physical findings. Wassermann and Kahn, and urinalysis negative; blood counts normal. In October patient developed cough and sputum, and râles appeared in right upper lung field. Efforts to get repeat x-ray of chest were unavailing until November 4, when film showed unfavorable progress, with more extensive lesions in upper one-fourth of right lung field, and a cavity in the lower portion of the involved area. Sputum examined 8 times, negative 7 times June to October, positive once, in November. In spite of persistent uncooperative attitude patient finally was hospitalized in Cook County Hospital on Jan. 14, 1942, but left against advice in May, 1942, and died at home one week later of advanced pulmonary tuberculosis, twelve months after initial examination and delivery.

Summary

1. One thousand consecutive patients attending the Prenatal Clinic of the Provident Hospital and Training School were examined for pulmonary tuberculosis by fluoroscopy and x-ray.

2. Eighteen cases, 1.8 per cent, of unsuspected clinically important tuberculosis and 11 additional cases, 1.1 per cent, of clinically unimportant reinfection tuberculosis, a total of 29 cases, or 2.9 per cent, were found by this technique. This incidence was found to be approximately the same as for other nonpregnant women of the same age groups examined at Provident Hospital.

3. These findings are compared with those reported by Eisele and associates¹ at the Chicago Lying-in Hospital, where the incidence of unsuspected clinically important tuberculosis was 1.0 per cent. It is

negative, blood counts normal. Sedimentation rate 11 mm. in thirty minutes, 18 in sixty minutes (Cutler). Admitted to Provident Hospital Feb. 23, 1940, normal girl born March 1 after episiotomy, usual repair. Fever of 99.6° to 100.0° F. from March 4 to 18, when patient left hospital. Repeat x-rays of chest on February 29 and March 13 showed unfavorable progress of tuberculous lesions. Attempts were made to arrange for sanatorium care elsewhere but patient and family were uncooperative. Patient became more acutely ill at home and was admitted to Cook County Hospital on May 23, 1940, and died there of advanced tuberculosis on Aug. 29, 1940, seven months after initial examination and six months after delivery.

CASE 2.—D. M., aged 17, gravida ii, para i, reported to Prenatal Clinic Feb. 5, 1940, gestation six months. Previous pregnancy terminated April 25, 1939, normally except for first degree perineal laceration, with usual repair. Infant died at four days, cause unknown. Mother was found to have active tuberculosis, and patient was x-rayed as contact of her mother by Chicago Municipal Tuberculosis Sanitarium Dispensary on Aug. 22, 1939, but no definite tuberculosis was found at that time. Fluoroscopy at Provident Hospital at time of first prenatal visit, Feb. 5, 1940, showed minimal bilateral upper lobe exudative tuberculous lesions. Past history at Provident Hospital irrelevant: infected adenoids in January, 1937; skin infection of foot, June, 1938; laceration of scalp, December, 1938. Patient uncooperative, persuaded with difficulty to return to hospital on March 3, 1940, for chest x-ray which confirmed fluoroscopic impression of minimal predominantly exudative bilateral apical and subapical tuberculosis without cavitation; and to Chest Clinic on April 2, 1940. Patient denied all symptoms, physical examination of chest was negative. Wassermann and Kahn, and urinalysis negative; blood counts normal. Admitted to Provident Hospital May 12, 1940; delivered a normal 9 pound male same day, with second degree perineal laceration, usual repair. No post-partum complications. Repeat x-ray of chest May 15, 1940, showed no change in pulmonary lesions. No sputum available for examination. Seen again in Chest Clinic June 11, no change. Sanatorium care nevertheless recommended, but patient and family uncooperative. In May, 1940, patient was in Cook County Hospital for a short time but left against advice. In August, 1940, it was learned patient had returned to work, but by March, 1941, she was much worse and reported to the Kenwood Dispensary of the Municipal Tuberculosis Sanatorium, where artificial pneumothorax was begun. Soon afterwards she was admitted to the sanatorium, but in spite of the pneumothorax and sanatorium care the tuberculosis steadily progressed unfavorably, and patient died of advanced tuberculosis there on Nov. 28, 1941, 22 months after initial examination; 18½ months after delivery.

CASE 3.—R. J., aged 26, gravida iii, para ii, reported to Prenatal Clinic Jan. 16, 1941, gestation four months. Two previous pregnancies terminated normally in 1934 and 1935, without complications, both children living and well. Fluoroscopy at Provident Hospital on Jan. 9, 1941, one week prior to prenatal visit, and chest x-ray January 11 showed minimal bilateral apical predominantly exudative tuberculosis. Repeat x-ray February 3 confirmed these findings. Seen in Chest Clinic Jan. 21, 1941, no complaints except loss of 7 pounds in weight in two

following treatment, a second obviously important consideration is the choice of a reliable minimum number of negative cultures to be required before the patient is released as bacteriologically cured. Of significance also is the spacing of such cultures, especially with relation to the menstrual cycle. A review of the literature, however, indicates that the choice of a bacteriologic standard of cure is in most instances haphazard and arbitrary and without any rational basis beyond the experience and convenience of the investigator. For example, the number of negative cultures required for release of the patient following treatment may vary from none at all^{5, 17} to as many as 17 or more.^{3, 7, 14} In the male, the published criteria of cure are astonishingly varied. To illustrate this point Table I lists the criteria of cure of gonorrhea in the female in some of the more recent literature reports.

TABLE I. CRITERIA OF CURE OF GONORRHEA IN THE FEMALE

INVESTIGATORS	CRITERIA OF CURE			
	SMEARS	CULTURES	POST-TREATMENT OBSERVATION	CLINICAL REQUIREMENTS
Committee on Gonorrhea in the Female (USPHS) June, 1940 ¹	12*	12*	4 months	Disappearance of signs and symptoms
Committee on Gonorrhea in the Female (USPHS) June, 1941 ¹	6	6	Through 2 menstrual cycles	
Lewis ¹² (1940)	8-10	4	4 months	"Clinical cure"
Smith and Deakin ¹⁹ (1942)	6*	6*	Through 2 menstrual cycles	"Clinical cure"
Mahoney, et al. ¹⁶ (1940)	3 (min.) to 10 or more.	3 (min.) to 10 or more.	Variable	"Remission of clinical evidence of disease"
Moffett ¹⁷ (1940)	6-8	None	Through 2 menses	
Jacoby ⁸ (1941)	12*	12*	5 months	Absence of all clinical signs and symptoms
Mahoney, et al. ¹⁴ (1941)	17*	17*	2 months	Absence of signs and symptoms
Fogan (and Newsome) (1939) ⁴	3	3	3 months	
Fletcher, et al. ³	12-36*	12-36*	3-9 months	
Grodberg and Carey ⁵	3*	None	1 month	At least 1 pre- or post-menstrual smear
Hesseltine, et al. ⁷ (1941)	17	17	3 months	Cultures before, during and following menses

*Both urethral and cervical cultures specified.

Recently Mahoney and colleagues¹⁵ have demonstrated the necessity of repeated culture for detection of the gonococcus in chronic infections. Of 367 prostitutes having negative cultures on entrance into a closed institution, 61 (16.6 per cent) yielded subsequent positive cultures, this in spite of the fact that 10 to 20 culture plates were inoculated at each examination.

concluded that the difference is probably due more to the different economic and social status of the two groups than to race, or to a slight difference in their age distributions.

4. The finding of so high an incidence, especially in the Negro in whom tuberculosis tends to run a more unfavorable course, serves to confirm the contention that routine chest roentgenologic examinations should be an indispensable part of the prenatal care of Negro pregnant women.

The patients seen at Provident Hospital were under the supervision of Dr. Pedro M. Santos, Senior Attending Obstetrician. The fluoroscopic was carried out under the direction of Dr. Robert G. Bloch, Professor of Medicine, the University of Chicago. To them, and to others who assisted in the fluoroscopies at various times, the authors wish to extend their thanks and acknowledgment for cooperation received.

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A MINIMUM BACTERIOLOGIC CRITERION OF CURE OF GONORRHEA IN WOMEN*

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THE problem of establishing cure of gonorrhea in the female with a reasonable degree of assurance has always been difficult, both from the clinical and the bacteriologic viewpoint. A further complication to this uncertain problem is the tendency of certain of the sulfonamides to effect clinical subsidence of the infection without elimination of the gonococcus. Reports of a carrier state or latency following sulfonamide therapy, and sulfanilamide especially, have been frequent.^{2, 6, 12, 18, 19} Such infections not only constitute a serious public health problem but are also potentially capable of acute and severe exacerbations at a later time.

The general unreliability of the stained smear for the detection of the gonococcus in female infections, and particularly in chronic and latent conditions, is well recognized; so that cultural methods, where available, are more generally relied upon to establish cure and to detect residual infection. Assuming that clinical cure has been established

*This study was supported in part by funds of the United States Public Health Service and the Venereal Disease Division of the Texas State Department of Health.

was complete clinical cure obtained; hence six consecutive cultures are counted in this case. Patient 5 became an asymptomatic carrier following an initial irregular course of sulfapyridine and was believed to have harbored the infection continuously during the entire period of observa-

CASE	CULTURE RESULTS & TREATMENT																							
1	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
					SP	C																		
2	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
					SP	C																		
3	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
					SP	SP	ST	F	C															
4	+	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
					SP			ST	C															
5	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
					SP	C		SP				ST							ST					
6	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
					SP	ST																		

+ positive culture. C - clinical cure

- negative "

L - lapse in observation

SP - sulfapyridine

ST - sulfathiazole

F - fever therapy

— period during which patient was believed to be infected.

Fig. 1.

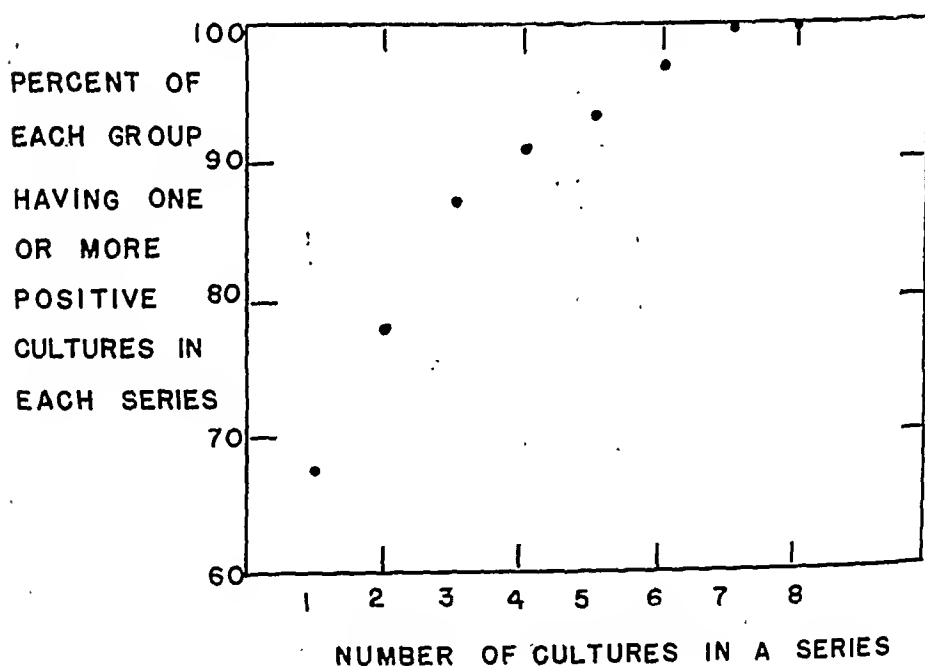


Fig. 2.

tion. Persistent clinical evidence of gonorrhea in Patient 6, despite negative cultures following chemotherapy, necessitate inclusion of all eight cultures in this series.

The culture results of each patient were tabulated in the ascending order of the number of successive cultures obtained during the period

The problem may be stated as the desirability of determining the minimum number of cultures required during a minimum observation period to detect a maximum of residual infections. Although the studies reported here are preliminary and are concerned only with the bacteriologic aspect of the problem, it is hoped that they will stimulate further attempts to establish a safe standard criterion of cure in both female and male.

Procedure

The patients involved in this study were treated and observed in the out-clinic of the John Sealy Hospital, a procedure which unavoidably introduces an error of considerable magnitude in the following data. The usual routine consisted of:

1. Clinical and bacteriologic diagnosis of gonorrheal infections;
2. Treatment with sulfonamides;
3. Culture and hematologic examination during treatment;
4. Bacteriologic tests at weekly intervals for two to four months after completion of therapy.

Many patients failed to complete the prescribed course of treatment or the follow-up, and a relatively high proportion suffered recurrences, either from relapse or reinfection. On the other hand, many cases have been followed for a year or more.

Each cervical swab was plated directly on one plate of Proteose 3, hemoglobin agar,* which was incubated and examined by the accepted methods. Positive cultures were confirmed by the usual differential tests, particularly if there was reason to doubt the identity of the organism. These results have been reported elsewhere.¹¹

In a large number of cases, two or more cultures were obtained from the patient before instituting chemotherapy. In many other instances, a succession of two or more cultures was taken over a period during which the patient was believed to be infected regardless of treatment received. Some of these patients constituted proved sulfonamide-resistant cases; others represented treatment failures because of inadequate or irregular treatment, or for other reasons.

Results

In order to arrange the data for analysis, each patient's record was studied in an effort to determine how many successive cultures were obtained during the period in which the patient exhibited any evidence of infection, either bacteriologic, clinical, or epidemiologic. Those patients having clinical or bacteriologic recurrences following treatment were considered as having been infected continuously, regardless of the number of intervening negative cultures, unless strong evidence of reinfection could be established. Thus, the number of successive cultures taken from infected patients varied from two in many individuals to thirty or more in a few. To illustrate, the culture protocols of 6 patients are presented:

In Case 1, clinical cure followed the three successive positive cultures obtained before sulfapyridine therapy was instituted. In Case 4, reinfection was not proved following the first course of sulfonamides, nor

*A supplement of unautoclaved liver or yeast extract is required to supply a thermolabile nutritive necessary for growth of a significant proportion of the strains of gonococcus encountered in our studies.²¹

5. The probable inclusion of some cases not infected during a period of the study and exclusion of others who may have harbored residual infection.

6. The proved occurrence of sporadic positive cultures in a long series of negative cultures in some individuals (15).

7. The failure to consider the time element in the follow-up studies.

8. Difference in culture media and bacteriologic technique will influence the yield of positive cultures in various laboratories.

The studies of Mahoney and others,¹⁵ which were conducted in the House of Detention for Women of the Department of Correction of New York City, are subject to far greater control than is possible in clinic studies. Only in some such closed institution, in which the variables are reduced to a minimum, could a study of this type be conducted adequately. The demonstration by these investigators of the occurrence of sporadic positive cultures following a long series of negative tests, and of the permanent reversal of culture positivity in a high percentage of untreated chronic cases, emphasizes the need for great conservatism in the interpretation of results of negative bacteriologic tests, particularly in the presence of any clinical evidence of infection. These results do not, however, nullify the need for, nor the desirability of some *minimum* bacteriologic standard for routine follow-up observation. Nor should the clinician dogmatically assign any residual pathologic signs or symptoms following treatment to a persistent gonorrheal infection in the event of repeated negative cultures. The causes of chronic leucorrhea and pelvic pathology are not only many and varied, but present also an extremely difficult problem of differential diagnosis from chronic gonorrhea, considered from the clinical standpoint alone.

It is recognized that no practical number of cultures will detect *all* residual infections, since, as Mahoney¹⁵ and Lewis¹³ have pointed out, the gonococcus may recede to the deep glandular crypts of the cervix, to be discharged at sporadic and infrequent intervals. Therefore, the foregoing results should not be interpreted to mean that 6 to 8 cultures will detect 100 per cent of all infections, but rather a *majority* of residual infections.

Any satisfactory follow-up should extend for a sufficient length of time. It is highly improbable that six cultures taken on successive days following cessation of chemotherapy would be as effective in detecting residual infection as six cultures at weekly intervals, including one or two menstrual cycles. The studies of Fletcher, Gibson, and Sulkin³ bear out this point. In a series of 194 cases, six weekly cultures following therapy sufficed to detect all probable relapses, although the observation period was extended for thirty-six weeks. Of three recurrences at the fifteenth week, "the possibility of reinfection was established before they were listed as new cases."

in which the patient was believed to be infected. Each of the longer series (e.g., Patient 5 above) was subdivided into smaller series, having 2, 3, 4, etc., consecutive cultures. In Table II are recorded the number of series in each group having two consecutive cultures per patient, three consecutive cultures, and so on up to the group having eight or more successive cultures per patient. Thus, there were 156 series in the group having four successive cultures; of these, four consecutive cultures yielded *at least one* positive culture in 91 per cent of these cases. On the other hand, of the 54 series of seven consecutive cultures from infected individuals, the gonococcus was detected at least once in every series.

TABLE II. PERCENTAGE OF INFECTIONS DETECTED BY CULTURE

NO. OF CULTURES IN EACH SERIES	NO. OF SERIES IN EACH GROUP	NO. OF SERIES IN EACH GROUP WITH AT LEAST ONE POSITIVE CULTURE	PER CENT OF SERIES IN EACH GROUP WITH AT LEAST ONE POSITIVE CULTURE
1	1270	860	67.7
2	587	481	78
3	262	229	87.4
4	156	142	91
5	95	89	93.7
6	68	66	97.2
7	54	54	100
8	36	36	100
(or more)			

By plotting the percentage of each group having one or more positive cultures in each series of consecutive cultures against the number of successive cultures in the series, a curve is suggested. Of the total number of cultures taken (1,270), 860, or 67.7 per cent, were positive; a single culture, therefore, might be expected on this basis to detect 68 of 100 infections. If 2 consecutive cultures are obtained, 78 of 100 would yield one or both cultures positive; with 4 consecutive cultures, from 1 to 4 positive tests might be expected in 91 of 100 cases.

A point is soon reached, however, at which the law of diminishing returns becomes operative, so that the percentage of additional residual infections detected by more than 6 or 7 successive cultures would scarcely be worth the added effort. This is the point which might be adopted as a minimum bacteriologic criterion of cure.

Discussion

In presenting the foregoing data and proposing, for example, that six successive negative cultures be adopted as a reasonably safe minimum for release of treated cases, the authors realize that a formidable array of errors and omissions are involved. To list a few:

1. The impracticability of applying to every individual the results of group analysis.
2. The unreliability of any data obtained in dispensary studies relative to relapse and reinfection.
3. The use of culture data from both treated and untreated cases.
4. The arbitrary method of arranging the data and the decisions to include or exclude certain cultures from a series.

CALCIUM AND QUININE IN LABOR AND POST-PARTUM HEMORRHAGE

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QUININE has long been employed to stimulate contractions in the pregnant uterus, but has fallen into disrepute somewhat in recent years because of reported ill effects on babies.

Calcium has been credited with various effects upon different organs. It is used for relaxing such organs as the gall bladder and has enjoyed a certain amount of popularity as an antispasmodic in dysmenorrhea. Its effect varies in different animals and often in different concentrations.

The pediatrician and internist are familiar with tetany occurring in children and chronic nephrities where the serum calcium falls below a level of 9 mg. per cent. In ether anesthesia it has been shown that serum calcium drops but not to the level causing tetany. Tetany from over ventilation is probably caused by a relative alkalosis and the resulting relative calcium deficiency.

Body calcium is found fixed in certain tissues and as serum calcium, which consists of two physiologically distinct fractions which have been termed diffusible and nondiffusible. The amount and state of the body calcium is dependent not only upon the amount ingested but also upon certain vitamins, notably vitamins A and D, as well as such hormones as para-thor-mone. The diffusible form of serum calcium will pass through artificially prepared membranes. It ranges in concentration from 4.5 to 5.5 mg. per cent. A small fraction of this diffusible calcium is in the ionized form. In normal pregnancy there is a decrease in serum calcium but rarely below the accepted normal. This alteration is evidenced by progressive decrease in the nondiffusible fraction and a slight increase in the diffusible fraction. Calcium will restore the contractility of smooth muscle that has been temporarily depressed by other ions. The normal serum calcium level is 9 to 11 mg. per cent; however, it becomes toxic only when a level of 23 to 26 mg. per cent is reached.

In Danforth and Ivy's work on the effect of calcium on uterine contractility they showed that an optimum concentration of calcium was necessary to maintain the contractility of the uterus. They also showed that such agents as pituitrin and ergot were not as effective if there was a deficiency of serum calcium.

Mussey studied the effect of calcium gluconate upon 27 pregnant patients and concluded that it was an efficient oxytocic.

Artificial provocation measures, i.e., chemicals and vaccines, have been abandoned largely as tests for cure. The provocative effect of menstruation, however, seems rather well established,^{5, 7, 9, 10, 20} and unless a more thorough reinvestigation of the problem should indicate otherwise, it is best included among the tests for cure, with one or two postmenstrual cultures being obtained during the observation period.

Summary

1. Repeated cultures may be necessary to demonstrate the gonococcus in chronic and latent infections, particularly following chemotherapy.
2. Negative smears have no value as a bacteriologic test for cure, and indeed the smear might well be abandoned altogether for this purpose.
3. On the basis of data presented, it would appear that six successive cultures will detect a high percentage of residual gonococcal infections.
4. It is suggested that a *minimum* of six negative cultures at weekly intervals, including one or two postmenstrual cultures, be obtained before a patient is released from observation.

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There were 2 dead babies. One was in the case of the patient who had a large baby with cephalopelvic disproportion and Bandl's ring. In the other the mother had a severe fall preceding delivery, and no fetal heart-beat tones were heard shortly thereafter.

There were 2 asphyxiated babies. One was a premature infant who had a precipitate labor and the other had a difficult forceps delivery.

There were no ill effects that could be attributed to the quinine.

Calcium Gluconate

Calcium gluconate alone was given to 12 patients to stimulate labor pains. Six were primiparas and 6, multiparas. The average number of pregnancies was 1.83. The average age was 24.16 years. Nine of them were at term, one two weeks overdue, one seven months, and one three months' missed abortion.

The term patients all had cephalic presentations. Ten had no cervical dilatation, while 2 had 3 cm. to 4 cm. dilatation. The membranes were ruptured in 4 and intact in 8. Three of those with intact membranes responded to calcium gluconate, and 2 others had some pains which faded out. The three months' missed abortion had no effect from the medication.

The initial dose was 4 c.c. to 5 c.c. intravenously. The average total dose was 8 c.c. of the 10 per cent calcium gluconate solution.

Two patients had precipitate labors following the medication. There was one asphyxiated seven months' baby. There was one dead baby, the death of which was apparently caused by a prolapsed cord.

These 12 pregnancies were terminated as follows: 10 delivered spontaneously, one was delivered by version and extraction, and one by forceps.

There was one Bandl's ring in an overweight colored primigravida who had a large fetus. The fetus was delivered by version and extraction with difficulty after adrenalin was given and she was under deep anesthesia.

The one forceps delivery was occasioned by cephalopelvic disproportion.

Calcium Gluconate in Hemorrhage

Calcium was used fourteen times in 4,000 deliveries to check hemorrhage in atonic uteri.

In the post-partum patients who received calcium for hemorrhage, the customary post-partum medication, usually pitocin and ergot, had, as a rule, been given at the end of the third stage with little or no effect. Some of them had been given a second dose of ergotrate intravenously. In addition to the medication, massage had been used in most instances without result. No attempt was made to stop hemorrhages from uteri with lacerated cervixes or from vaginal lacerations by the use of calcium gluconate. It was given intravenously and usually in doses of 5 c.c. Three patients received 10 c.c. but the results were apparently no different.

In this group of patients the hemorrhage occurred in some immediately after delivery and in others as late as nine hours after delivery; still others had immediate post-partum hemorrhage and bled again some time after returning to the ward.

There were 7 primiparas and 7 multiparas. The high incidence of primiparas is probably explained by the larger number of operative

Our patients were divided into three series: one group received calcium and quinine in combination, either intramuscularly or intravenously, a second group received calcium gluconate intravenously, while a third group received calcium gluconate intravenously after the third stage, in case of hemorrhage from a relaxed uterus.

The terminology used to describe the effects is as follows: no results means no uterine contraction in response to the medication, fair result means contractions for awhile which subsided without the patient coming to delivery, good result means that existing contractions were either increased or that contractions were initiated and lasted until delivery was accomplished.

The patients in whom we attempted to induce labor varied from seven months' gestation to five weeks overdue. In some the membranes were intact and in others they were ruptured.

Analysis of Results

Thirty-five patients received calgluquine,* a preparation consisting of calcium gluconogalactogluconate 0.1375 Gm. and quinine gluconate 0.06 gr. (0.037 Gm. of anhydrous quinine base) per c.c. There were 18 primigravidas and the rest multiparas. The average number of pregnancies for the group was 1.71 per patient. The average age of the group was twenty-seven years. In 13 patients the membranes were ruptured, and intact in 22. Twenty-four had no dilatation of the cervix, while 11 had varying degrees of dilatation. There was 1 breech presentation, the rest were cephalics.

The average initial dose was 4 c.c. and the average total dose per patient was 8 c.c. Four patients received the medication intravenously while the rest received it intramuscularly.

There was good response in 20 patients. Ten of these were from the 13 who had ruptured membranes. Only 10 of the 22 with intact membranes gave satisfactory response.

In 7 patients, who were from seven to eight months' gestation, 3 were not in labor but early delivery was desired for medical reasons. None of them went into labor after the calgluquine. In four patients of seven to eight months' gestation, 2 were having irregular pains and 2 were not in labor. All of them went into satisfactory labor shortly after the medication, and delivered.

There were 4 mild toxemias. Among the term patients only one responded to calgluquine, and she was well advanced in labor when it was given. Two of them had previously been given magnesium sulfate parenterally. Whether there was an antagonistic action, thus preventing the onset of labor, we do not know.

The 35 labors terminated as follows: 22 spontaneous deliveries, 9 forceps deliveries, 2 cesarean sections, 1 version and extraction, and 1 breech extraction. Of the forceps deliveries, only 3 were necessary, the remainder were for teaching purposes.

Two Bandl's rings were found. Both were in patients who had long labors and "stalled" because of cephalopelvic disproportion. One was terminated by version and extraction and the other by cesarean section. Neither of these patients should have been given a uterine stimulant.

*Calgluquine is a product of the Sandoz Chemical Works, Inc., New York, N. Y.

calgluquine. The response was more prompt than the intramuscular route, in that some of these had precipitate labors.

3. The best results were obtained where the patients had ruptured membranes or were already having mild pains.

4. No ill effects on the babies from the quinine were noted in this series; however, the dose was small.

5. Three Bandl's rings were found. All had more or less cephalopelvic disproportion which was probably the principal factor in the Bandl ring.

6. Patients with post-partum hemorrhage from atonic uteri that had not responded to the usual oxytocics had, as a rule, a marked hardening of the uterus and a lessening of the hemorrhage immediately after receiving intravenous calcium gluconate.

Discussion and Conclusions

Calcium salts alone or in combination with small amounts of quinine are useful in initiating contractions in patients with ruptured membranes. They are also valuable in patients with "piddling" labors. Care should be exercised that a cephalopelvic disproportion is not present as these drugs are contraindicated here. One should be careful to distinguish between a "stalled" labor from dystocia and one of the "piddling" type that has ineffectual pains. If quinine is to be used, the history of drug dyscrasias should be learned.

Calcium is to be avoided, or at least used very carefully, in patients on digitalis or related drugs.

The most gratifying results were obtained in the management of post-partum hemorrhage. In some cases dramatic results were obtained. In other cases the uterus had partially contracted but bleeding continued with a trickle until calcium was given, then the uterus contracted tightly. The one case of incomplete abortion was not benefited.

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deliveries in this group. Their average ages were 21.33 years and was irrelevant.

Seven delivered spontaneously, 6 had forceps deliveries, and 1 was a breech extraction. Of the spontaneous deliveries, 1 had a four months' abortion and retained the placenta. She bled when the placenta began separating.

The weights of the babies from the women at or near term varied from 2 pounds 7 ounces to 10 pounds 4 ounces. There were no twins or polyhydramnics.

The length of the labor was irrelevant. In some it had lasted over a couple of days while in others it had been very rapid.

There was one lacerated cervix which was repaired after manual removal of the placenta. The uterus failed to contract well.

Six patients had surgical ether, 1 surgical chloroform, 3 obstetric chloroform, 1 cyclopropane, 1 local anesthesia, and 1 nothing at all.

The higher incidence of hemorrhage occurring after ether might be explained by the fact that it was the most commonly used anesthetic for operative obstetric procedures. All of the ether anesthetics were terminated by operative means. One of the chloroform patients and the patient with local anesthesia had operative deliveries. The remainder were spontaneous.

The effect of the calcium gluconate is hard to determine in some few cases; however, in the majority, it was clear-cut. The patient who had an incomplete abortion and retained placental tissue did not respond at all. She is the only one that required packing.

The usual routine was to give pitocin, $\frac{1}{2}$ c.e., at the end of the second stage and ergotrate, $\frac{1}{320}$, at the end of the third stage intramuscularly.

In 8 patients there was an immediate post-partum hemorrhage following the third stage, which did not stop after ergotrate. Four received an additional dose intravenously, with partial or no response. The uterus remained baggy and there was a continual stream of blood which varied from a trickle to a gush. Calcium gluconate usually, in 5 c.c. doses, brought about a marked hardening of the uterus with a prompt decrease in bleeding in 7 of the 8 patients.

In the remaining patients the hemorrhage started from twenty minutes to nine hours after delivery. They usually left the delivery room in good condition. Two had some excess bleeding at the time of delivery. When the bleeding was discovered on the ward, they were given intramuscular ergotrate, $\frac{1}{320}$, which was followed by intravenous calcium gluconate, 5 c.c., in fifteen minutes to thirty minutes if bleeding continued. Four of the 6 had prompt diminution of the flow. However, the exact effects are hard to evaluate as the ergotrate may have been slow to act in some cases. The bleeding in some would probably have checked had we been able to wait. But in others the effect of the calcium was dramatic. Five of this delayed group of bleeders had been given surgical ether for operative deliveries.

Summary

1. The combination of calcium and quinine was apparently a little more effective than calcium gluconate alone.
2. The intravenous route of administration alone was used in the patients receiving calcium gluconate, and in 6 of the patients receiving

CASE 2.—M. R., aged 32 years. *Chief complaint:* painful menstruation. *Diagnosis:* dysmenorrhea, cervicitis, parametritis. Prior to the menstrual period in February, 1941, the patient received six injections of testosterone propionate, 10 mg. each, and the flow was slightly less painful. Before the period in March, due to external circumstances, she received only three injections (30 mg. of testosterone propionate). Menstruation in March was four days early and was again severely painful. Before the next period, ten injections (100 mg. of testosterone propionate) were given which, however, afforded no relief. Treatment was therefore discontinued.

CASE 3.—S. W., aged 24 years. *Chief complaint:* severe pain during the first two days of each menstrual period. Prior to the period in July, 1940, the patient received four injections (40 mg. of testosterone propionate) and pain during the menstrual period was slightly less severe. Two injections (20 mg. of testosterone propionate) were given before the next menstrual period with subsequent reduction in pain of approximately 50 per cent. Three injections (30 mg. of testosterone propionate) were given before the September menstrual period, but they did not, however, result in improvement. Although no hormone therapy was given prior to menstruation in October, this flow was entirely painless. During the following cycle, prior to menstruation, patient received four injections (40 mg. of testosterone propionate) with the result that pain during the menstrual flow was again diminished by about one-half. During the next two cycles treatment was omitted, but improvement continued. The patient was not seen again until November, 1941, at which time she was in the fifth month of pregnancy.

In some of the dysmenorrhea cases, efficacy of methyl testosterone, given by mouth, was evaluated. The dosage schedule was one 10-mg. tablet t.i.d. An attempt was made to determine the ratio of effectiveness between testosterone propionate parenterally and methyl testosterone orally. The following case report will illustrate the method followed in such a determination.

CASE 4.—E. K., aged 26 years. *Diagnosis:* severe dysmenorrhea. Prior to the menstrual period in February, 1941, the patient received eight injections of testosterone propionate, 10 mg. each. Pain during the ensuing menstrual flow was diminished by approximately 75 per cent. No medication was given during the following menstrual cycle, and the flow was just as painful as it was before institution of male hormone therapy. This patient was then given methyl testosterone orally. A total of 63 tablets, 10 mg. each, was ingested during the April cycle, 48 of which were taken during the second half of the cycle. Menstrual pain was reduced by approximately 50 per cent. During the next cycle, 76 tablets were ingested with 75 per cent improvement. Here again, 48 tablets, i.e., 480 mg. of methyl testosterone, were taken during the second half of the cycle. It will be noted that this compares with the dosage of 80 mg. of testosterone propionate administered parenterally. Improvement was maintained during menstruation in June and July without any medication during the cycles. Menstruation in August was again characterized by severe pain necessitating bed rest and hypnotics.

CLINICAL EVALUATION OF TESTOSTERONE PROPIONATE AND METHYL TESTOSTERONE IN DYSMENORRHEA AND MENOMETRORRHAGIA

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PAINFUL menstruation and functional uterine bleeding have always presented major therapeutic problems in gynecology. Male hormone preparations have been used in the treatment of these disorders by a great number of investigators with varying success. This report is concerned with the effects and results obtained by the administration of testosterone propionate* and methyl testosterone* in a series of 20 cases of dysmenorrhea and a series of 15 cases of menorrhagia or menometrorrhagia.

Dysmenorrhea

No effort was made to select these cases. Patients were taken consecutively just as they appeared in the clinic. The treatment was planned to consist of a 10 mg. injection of testosterone propionate administered intragluteally every other day, starting two weeks before the expected onset of menstruation. The therapy was followed so far as possible. However, since it necessitated visits to the clinic on the part of the patients, there was some irregularity, i.e., deviation from the original plan. In appraising the results, two cases of the original series of 20 were omitted because of inadequate therapy due to lack of cooperation and incomplete observation. Of the remaining 18 patients, 4 experienced complete relief during the period of observation, 8 experienced partial relief, the reduction of pain varying from 25 to 75 per cent; 6 experienced no improvement. The period of observation extended from two to seven months. Of the 12 patients who were relieved, pain recurred in 7 upon discontinuation of medication. The following case histories are given as typical instances:

CASE 1.—M. M., aged 32 years. *Chief complaint:* Painful menstruation. *Diagnosis:* dysmenorrhea, cervicitis, third-degree retroversion. Prior to the menstrual period in February, 1941, the patient was given eight injections of testosterone propionate, 10 mg. each, and the period in February was painless. No treatment was given during the next two menstrual cycles, and the menstrual flow at the end of each cycle was painless. For three days before the onset of menstruation in May, the patient had severe pain which was not relieved by sedatives.

*Testosterone propionate (Neo-Hombreol) and methyl testosterone (Neo-Hombreol [M] Tablets) were supplied by Roche-Organon, Inc., Nutley, New Jersey.

Alleviation of painful menstruation by administration of male hormone in smaller doses therefore could be on the basis of reducing excessive contractions of the uterus.^{1, 2}

The hypothesis that menometrorrhagia may be due to excessive or unbalanced elaboration of estrogen is workable and rational in the light of present knowledge. On the basis of this hypothesis, the beneficial action of the male hormone in excessive uterine bleeding has been attributed to several effects, including suppression of estrogen production and inhibition of the anterior pituitary. However, in this dyscrasia as in dysmenorrhea, the inhibiting action of the androgens on rhythmic uterine contractility may be the reason for their value. In menometrorrhagia, the inhibition of uterine contractility has been shown to decrease the volume of blood flow to the uterus, hence the beneficial results. Furthermore, the androgens have a direct effect on the myometrium, bringing about constriction of the myometrial vessels, thus reducing the volume of blood flow.^{3, 4}

The recurrence of symptoms after cessation of therapy would seem to indicate that no permanent alteration in the hormonal balance of the patient had been effected by the therapy of the duration in this study.

Summary

Eighteen patients with dysmenorrhea and 9 patients with menorrhagia and menometrorrhagia were treated with testosterone propionate and methyl testosterone. Complete relief of symptoms was experienced by 4 and improvement by 8 of the dysmenorrhea patients and complete relief by 6 and improvement by 2 of the menometrorrhagia patients. Thus, androgen therapy was completely or partially effective in 67 per cent of the dysmenorrhea cases and in 88 per cent of the menometrorrhagia cases. Practically, in all instances there was a recurrence of the original ailment after discontinuation of treatment at varying intervals. Oral androgenic therapy, if administered in adequate dosage, yields the same result as parenteral therapy.

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Menorrhagia and Menometrorrhagia

The treatment in this series of cases was planned to consist of 25 mg. injections of testosterone propionate administered intragluteally every other day, starting at least two weeks prior to the expected onset of menstrual flow. However, this plan could not be followed in some cases. If patients presented themselves during the period of excessive bleeding, whether at or between periods, the flow abated promptly after institution of treatment. A single 25 mg. injection frequently was followed by a lessening of the flow. Six patients of the original group of 15 could not be followed for longer than one month and, therefore, are not considered in the final appraisal. Of 9 patients remaining, 6 experienced complete relief from excessive bleeding, 2 were partly relieved, and 1 showed no change. The patients were observed two to nine months after institution of therapy.

The following case histories are illustrative:

CASE 5.—M. A., aged 33 years. *Chief complaint:* Profuse bleeding over a period of seven days. In May, 1941, prior to the menstrual period, the patient received four injections (100 mg. of testosterone propionate). The subsequent period lasted four days and the flow was markedly decreased. No treatment was given during the June cycle and the ensuing menstrual flow was again excessive over a period of seven days. No therapy was employed during the next menstrual cycle either, and here, too, the flow was profuse and lasted eight days.

CASE 6.—E. B., aged 29 years. *Chief complaint:* Excessive menstrual flow, uterine bleeding between periods. Four injections (100 mg. of testosterone propionate) were given to this patient prior to the menstrual period in July, 1941, which lasted four days and was moderate. Also, there was absence of metrorrhagia. No treatment was given during the next cycle, but nevertheless the following menstrual period lasted only four days and was moderate. The same was true of still the next period, although no medication had been employed. Menstruation during October, November, and December likewise was not preceded by any medication and in each instance was slightly more profuse but considerably improved compared with the status before institution of therapy.

Symptoms of masculinization were noted in two patients. There was very slight hirsutism on the face which disappeared shortly after discontinuation of medication. One patient complained of nausea and vomiting following an injection.

Discussion

Since dysmenorrhea is the manifestation of various pathologic conditions, it cannot be anticipated that male hormone therapy will alleviate painful menstruation in every case. Various theories have been advanced as to the cause of functional dysmenorrhea. It seems likely that a disturbance in the normal uterine contractility during menstruation may be the underlying factor of this disorder. Evidence has been presented that male hormone in large doses suppresses uterine contractions.

While the skull is being opened, and the brain and supporting structures examined, the head is held over a pan so that the fluid which escapes is not lost. The brain after inspection in situ is removed into the same pan and any fluid remaining in the cranial vault is added. Two layers of fine meshed surgical gauze are immersed in water, wrung as dry as possible, and placed over the top of a wide-mouthed jar. The brain and all of the material within the pan are emptied into the cloth and the fluid is permitted to filter through. At the end of fifteen minutes the fluid is measured.

It is impossible to remove the brain without loss of blood from the cerebral vessels and dural sinuses. In order to estimate the proportionate amount of blood in the total fluid the cell volume of a representative sample is determined by use of a Wintrobe hematocrit tube.

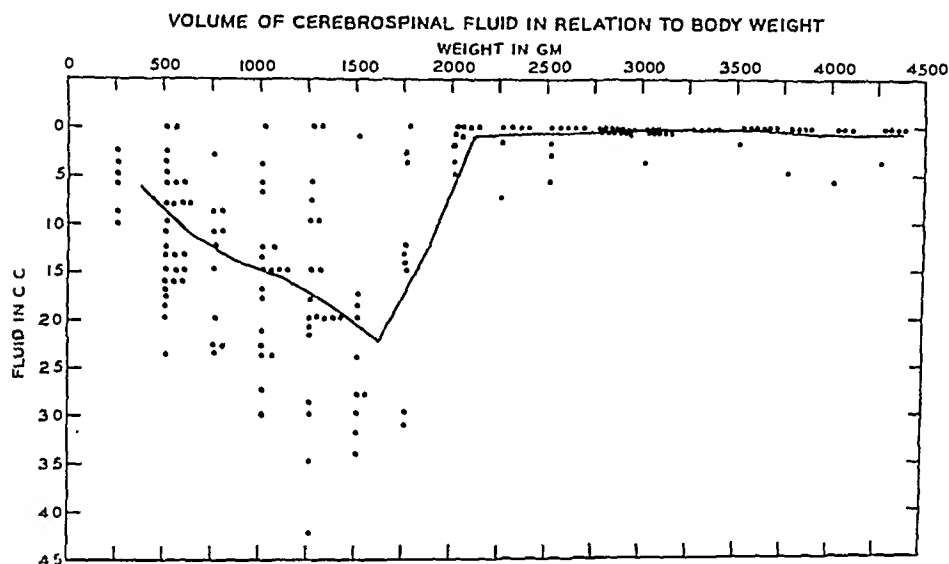


Fig. 1.

The cell volume is considered to represent one-half of the total blood volume, and the hematocrit reading is doubled to obtain the percentage of blood in the specimen. Minute particles of brain tissue often pass through the gauze and form a separate layer above the blood cells in the hematocrit tube. The amount of brain tissue may also be calculated from the percentage noted in the hematocrit tube. This, too, must be subtracted from the total volume. If, therefore, 15 c.c. of blood-tinged fluid is obtained, and the hematocrit reading is 4 per cent red blood cells and 2 per cent brain substance, the blood and brain tissue will amount to 10 per cent of the total measured volume. The corrected volume is consequently 13.5 c.c.

Results

The volume of intracranial fluid has been measured in 225 infants and fetuses. From this series we have eliminated all macerated fetuses, all infants living more than twenty-four hours, and all who died of intracranial hemorrhage, fetal hydrops, hydrocephalus, and other malformations in which excessive fluid may be found. In tabulating the various fluid volumes, it was noted that delivery by cesarean section is unusually frequent among the infants in whom the larger volumes are

THE NORMAL AMOUNT OF CEREBROSPINAL FLUID PRESENT WITHIN THE SKULL AT BIRTH

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THE amount of cerebrospinal fluid which can be demonstrated within the skull of a fetus or a newborn infant at necropsy varies normally in relation to the gestational age. An increase in fluid is occasionally observed which is independent of age and which, in some instances, seems to be related to the method of delivery.

We have been unable to find information concerning the actual amount of fluid present in the extracerebral spaces of the skull under either normal or pathologic conditions during fetal and early infant life. Scammon¹ states that the brain at birth fills the skull more completely than it does at any other time of life; then it occupies 97.5 per cent of the cranial cavity in contrast to 92.5 per cent in the adult. We have observed at necropsy that there is no visible fluid in the meninges of the majority of infants at term, and believe that the close approximation of the brain to the skull which is normally present occasionally causes an erroneous diagnosis of edema of the brain.

It is known that only a very little fluid can be obtained by spinal puncture within the first few days of life. However, the amount obtained from the spinal canal is not necessarily proportionate to the amount present within the skull. Levinson² found that from a few drops to 5 c.c. with an average of 3 c.c. could be obtained by spinal puncture on the first day of life, and that from 1.5 c.c. to 10 c.c. with an average of 6 c.c. could be obtained by cisternal puncture.

In order to measure the amount of fluid present within the skull at post-mortem examination we have devised a method which, although not entirely accurate, permits determination of the approximate amount of fluid and enables one to make comparisons of the amounts present in the heads of different infants.

Procedure

The scalp is reflected and the head is opened by cutting a large circular disc from each parietal bone in such a way that the dural sinuses remain intact. An inspection of the surface of the brain, and a general evaluation of the amount of blood and fluid within the head can then be easily made, a procedure which is much more difficult if vessels are incised in opening the skull.

OVARIAN AUTOGRAFTS

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OVARIAN autografting has been done in an attempt to supply ovarian secretion to those patients in whom surgical removal of both ovaries was necessary because of some nonmalignant ovarian disease. According to most authors the original technique for autogenous ovarian grafts was published in 1910 by Tuffier. Many reports favorable to this and modified techniques followed, although recently very little has been written about this procedure probably due in part to the advent of improved estrogenic therapy.

This survey shows that in many respects the results obtained have been good; however, it must be stated that the effects desired have not been completely achieved.

Material and Technique

This is a report of 38 cases of ovarian autografting. These cases have been taken from the record files of the Elizabeth Steel Magee and St. Francis Hospitals in Pittsburgh. This procedure was found to have been performed 38 times in twenty-five years, an average of 1.5 such operations per year in both hospitals. This rather small incidence is due largely to conservative ovarian surgery, although at times bilateral oophorectomy has been done when no ovarian tissue could be salvaged for grafting.

It is interesting that 23 of the 38, or 60 per cent, of the patients had previous pelvic surgery. In 9 of these patients one ovary had been removed. The ovarian pathology of these 23 cases was one of cystic change, the ovaries showing multiple small and large simple or follicular type cysts. Six of the other patients in this series showed pelvic inflammatory disease with peri-oophoritis and multiple follicular cysts of the ovaries. There were three patients with bilateral cystadenomas of the ovaries, two with large corpus luteum cysts of both ovaries, and one with bilateral dermoid tumors. Three patients with endometriosis were subject to ovarian autografting. The value of this procedure for cases of endometriosis subject to bilateral oophorectomy has been stressed by Counseller, although our records show that conservatism has been the rule for endometriosis, and whenever feasible, one ovary or a remnant of ovary has been left with some intact blood supply.

The age of the patients in this group varied from twenty-one to forty-three, the average age being thirty.

In this series, the earliest cases of ovarian autografting were done by Dr. R. R. Huggins in 1916. The technique then employed was similar to that of Tuffier. Large pieces of normal ovarian substance were implanted in the subcutaneous fat near the laparotomy incision. It was later learned that only the peripheral zones of these grafts survived, and that the central portions underwent necrosis. In eight of these cases the ovarian tissue was grafted into fat.

found. It was also observed that these infants and those who were delivered immediately after artificial rupture of the membranes made up the majority demonstrating the higher fluid volumes. The possibility therefore arises that delivery by these methods may be accompanied by an abnormal accumulation of fluid. (These infants are being studied separately and are to be reported at a later date.) In order to obtain a curve showing normal volumes of fluid, it was deemed advisable to eliminate all of those delivered by cesarean section, or immediately after artificial rupture of membranes. The resulting curve is similar to the one in which all cases are included, except that it follows a slightly lower course.

It would seem that these figures, then, may be considered representative of the normal amount of fluid present within the cranial vault in infants of varying birth weights. They are based on the findings in 170 selected infants and fetuses. The averages in relation to body weight are shown in Table I, and the range in relation to body weight in Fig. 1.

TABLE I. AVERAGE AMOUNT OF CEREBROSPINAL FLUID IN RELATION TO BODY WEIGHT

BODY WEIGHT GM.	VOLUME OF CEREBROSPINAL FLUID C.C.
250- 499	6.5
500- 749	11.4
750- 999	14.6
1,000-1,249	15.8
1,250-1,499	19.6
1,500-1,749	23.3
1,750-1,999	13.6
2,000-2,249	1.6
2,250-2,499	1.3
2,500-2,749	1.3
2,750-2,999	0
3,000-3,249	0.5
3,250-3,499	0
3,500-3,749	0
3,750-4,000	1.0

Conclusions

The amount of cerebrospinal fluid found within the cranial cavity at the post-mortem examination of 170 selected infants and fetuses is reported. The amount increases gradually from 7 c.c. in the weight group of 250 to 500 Gm., to 23 c.c. in the weight group of 1,500 to 1,750 Gm. Thereafter it falls abruptly, and in all infants and fetuses weighing over 2,000 Gm., practically no fluid can normally be demonstrated by the method used.

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not menstruate for two months. Thereafter she menstruated every month for three months, the flow lasting three days. Excessive bleeding recurred. Basal metabolic rates were found to be -16 per cent and -18 per cent. Five grains of thyroid substance were given daily, and the patient has menstruated normally three times in five months.

The duration of the menstrual activity in all the cases showed great variation. The number of years that these patients menstruated may be taken as an indication of the probable length of the life of the grafts. Three patients menstruated for five, seven, and eight years, respectively. There were two patients who menstruated for four years. One patient menstruated for two years, and another menstruated for one year. The period of follow-up for the others was brief and incomplete. The most significant finding of this survey has been that all the patients given multiple thin ovarian grafts into the rectus muscle were able to menstruate, and this seems to be the best evidence of the efficacy of the procedure.

Ovarian autografting has also been done in the hope of reducing the occurrence and the intensity of hot flushes. Twelve patients, or 46 per cent, of the 26 followed postoperatively had no hot flushes. Five patients in this group had hot flushes for two or three months until the grafts were able to establish function. In addition to these patients five others had mild hot flushes which were not disturbing enough to require therapy. This comprised a group of seventeen, or 65 per cent, which showed favorable relief from vasomotor waves. Four of these patients were observed over a period of several months, but the remaining thirteen were seen over a period of years. Nine of the 26, or 35 per cent, had severe hot flushes or hot flushes disturbing enough to require estrogenic therapy.

A greater number of the patients who had been subjected to hysterectomy reported severe hot flushes, and in addition this group showed a greater number receiving estrogenic therapy. Urinary estrogen assays were obtained in seven cases of this series. In all of these patients ovarian autografts had been placed in the rectus muscle. Considerable difficulty was encountered in having patients submit twenty-four-hour specimens of urine to the laboratory. The readings obtained on two patients in whom the uterus had been removed were 4 rat units (or less) per twenty-four hours in one patient; and 6 rat units (or less) per twenty-four hours in the second patient. The readings obtained on five patients in whom the uterus had not been removed were 6 rat units, 10 rat units, 15 rat units, 20 rat units, and 15 rat units per twenty-four hours, respectively. It is apparent that the patients not subjected to hysterectomy tend to have higher urinary estrogen levels.

It is well known that ovarian grafts, regardless of the site of implantation, tend to form cystic swellings. These structures are often painful, particularly those placed in the rectus muscle where there is the factor of greater mobility. Fifteen of the 26, or 57 per cent, of the patients who were followed postoperatively had no discomfort, no swelling, and no tenderness at the site of the ovarian implants. Five of the patients complained of swelling and tenderness at the site of the grafts at monthly intervals. Of the five, three did not have a hysterectomy, and the pain and swelling were reported to occur just before or during menstruation. Two patients subjected to hysterectomy complained of periodic slight swelling and tenderness, and two other cases noted tenderness and swelling which was not periodic.

From 1926 until the present time a modified technique has been used in which multiple thin grafts have been imbedded in one or both recti muscles. The greater available blood supply of the rectus muscle seemed to offer the grafts better opportunity for survival and function. Thin grafts were employed to avoid neerosis. The grafts were small slivers of ovarian tissue measuring from 5 to 10 mm. in length and from 1 to 2 mm. in thickness. They were all cut by scalpel from the cortex of normal appearing ovarian substance, because the greater number of remaining primordial ova are found in a small zone beneath the germinal epithelium. Other authors have strongly advised taking small grafts from the medulla or central portion of the ovary. There were no reasons given, however, for this modification. The ovaries after removal were always kept in a warm saline bath until the peritoneum was closed. The grafts were then cut and placed in small pockets within the rectus muscle which were made by sharply inserting a straight hemostat and spreading it to separate the fibers of the muscle. Each pocket was ample to bury completely one of the grafts, and from eight to sixteen grafts were implanted in each patient. There was at times a small amount of bleeding from the muscle which gradually subsided, and closure of the incision was completed with very little delay. In all cases, the incisions healed by first intention.

Analysis of Results

Adequate follow-up records were available in 26 of the 38 cases reported. Of these, 14 were patients in whom a supravaginal hysterectomy had been done. In the other 12 the uterus had been left in situ. Eleven of the twelve patients not subjected to hysterectomy were given thin ovarian grafts in one or both recti muscles, and all of these patients menstruated. Only one of this group received ovarian grafts into subcutaneous fat. In this patient cystic structures formed at the site of the grafts and excision of these transplants was eventually necessary. This patient never menstruated.

There was considerable variation in the character of the flow and the duration of the menstrual activity of each of the eleven patients treated by placing multiple thin ovarian grafts in the recti muscles. Some of the patients did not have a menstrual flow for two or three months following operation. This latent period has been discussed in other reports and seems to indicate the period of time required for the grafts to establish blood supply and functional activity.

There was some variation in the length of the menstrual cycles, although seven patients menstruated at monthly intervals. Occasionally one of these patients would report a missed period. The cycles of the other four patients showed more variation. One patient menstruated every three months, another every two to eleven weeks, and another menstruated twice in three months and no further report of her cycle was obtained. One other patient menstruated, but the interval between periods was never recorded.

The duration of the flow was recorded for six patients and usually lasted three days. There were two patients who had two-day periods.

The menstrual history of one patient is interesting. Before operation she had prolonged and excessive menstrual flow. Because of pelvic inflammatory disease bilateral salpingo-oophorectomy was necessary. Ovarian autografting was done. Following operation the patient did

transplanted into rectus muscle as evidenced by menstrual activity usually for years, in 100 per cent of cases with an intact uterus, and by microscopic demonstration of corpora lutea in grafts excised one and two years after implantation.

4. Sixty-five per cent of the 26 patients who were followed showed relief from hot flushes and did not require estrogenic therapy.

5. Painful ovarian grafts are usually due to the development of cysts, excision of which is difficult. Aspiration of the cysts is preferable.

I am deeply grateful to Dr. B. Z. Cashman for the greater part of the clinical material used in this report.

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DILATATION OF THE URETHRA FOR IRRITABLE VESICAL NECK

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THE various symptoms grouped under the heading "irritable vesical neck" are common complaints in gynecologic practice. The object of this paper is to record the results obtained in 100 consecutive cases of this condition treated by dilatation of the urethra.

There is no counterpart to the irritable vesical neck in male urology. It is a symptom complex rather than a clinical entity, for there are few objective findings. The urine is clear; there is no pyuria; the pathologic findings are inconstant and rare.

The four major symptoms are urinary frequency, urgency, burning, and a feeling of pressure. The yardstick of frequency is whether the patient can sit through a movie, a church service, or ride in a car. By urinary urgency is meant sudden desire to void, amounting at times to incontinence. The pressure sensation is midline and right over the bladder. The feeling is one of downward pressure as compared to the falling-out sensation of prolapse.

The patients in this series also complained of nocturia, terminal tenesmus, and small stream. Three in the group had coughing incontinence from associated relaxation of the pelvic fascia. Of the eighteen pa-

Four patients, or 11 per cent, had such pain and tenderness with the ovarian grafts that some type of interference was necessary. The operative record in each of these four cases did not indicate the size of grafts employed. It is possible that these grafts were larger and thicker than the thin ovarian grafts described in the technique above. In one of these cases the ovarian grafts had been placed in the subcutaneous fat. This woman never menstruated and she complained of severe hot flushes indicating very little functional activity. Following excision of the grafts her pain and tenderness disappeared.

In the three other patients multiple ovarian grafts had been placed in the rectus muscle. Because of the discomfort one patient was given deep x-ray therapy over the grafts and amenorrhea followed. Two patients were operated upon because of pain and swelling at the site of the grafts. In one case cystic ovarian tissue was excised twice during a two-year period following ovarian autografting. This patient continued to menstruate for three years and had no further discomfort. In the fourth patient regular menstrual flow continued for six years after removal of a cystic graft which had formed one year after implantation. In each case excision of these grafts was very difficult because of marked scarring and profuse bleeding. In the fourth patient cystic swellings reappeared twice at three-year intervals, and complete relief was obtained by aspirating the cysts with a 19 gauge needle. These cysts did not recur, and the functional activity of the grafts apparently was not disturbed. This type of treatment seemed preferable to surgical excision.

The ovarian transplants excised from two patients were examined microscopically. One transplant had been excised one year after implantation and showed activity because of the presence of an active corpus luteum. The ovarian graft in the second patient was excised two years after implantation and here again evidence of activity was shown by the presence of a regressing corpus luteum in a loose ovarian stroma. These corpora lutea were found in addition to larger cystic structures resembling follicular cysts.

There seems to be ample evidence to show that ovarian autografts can establish blood supply and develop some degree of function. The amount of ovarian secretion so supplied is probably small, yet every patient in this series with an intact uterus continued to menstruate following implantation of thin ovarian grafts in the rectus muscle.

This procedure can never be accepted as a substitute for any form of conservative ovarian surgery. It does offer definite benefit to those patients in whom bilateral oophorectomy cannot be avoided. Menstruation continues, menopause is often delayed for years, and the approach to menopause is more gradual in contrast to the abruptness of surgical menopause.

In the final analysis, the choice between ovarian autografts and estrogenic therapy is a matter of judgment for the individual surgeon.

Summary and Conclusions

1. Thirty-eight cases of autogenous ovarian grafts have been analyzed.
2. Ovarian autografts in fatty tissue are not successful.
3. Multiple (from 8 to 16) thin-sliced grafts from ovarian cortex into rectus muscle are recommended. These grafts functioned when

urethra. One should also add that the symptoms are worse in the morning and are aggravated by menstruation, although no statistics were kept on these two points.

As previously stated, objective findings are few. Only 4 patients had urethral earuneles, and 4 more had reddening of the meatus. If chronic urethritis and trigonitis cause earuneles and the irritable vesical neck, one would expect more earuneles and meatitis. It is possible that these patients were seen too early in the disease for such findings to be apparent. Two patients had gross urethral strictures, i.e., a 20 sound could not be passed without effort and resultant bleeding.

Cystoscopy was done only when the condition was resistant to treatment or when the duration of symptoms led one to feel that it would be wise to check at once. The major positive finding was chronic urethritis. By this is meant, red ridges starting at the vesical neck and running down the urethra. Table IV gives the findings.

TABLE IV

Chronic urethritis	5
Negative	4
Radium reaction	1
Polyyps at bladder neck and in urethra	2

Treatment for all of these patients consisted of gradual dilatation of the urethra with Walther dilators and instillation of some medication. Eighty-four had a 5 to 10 per cent Gomenal* in olive oil, while 16 had 1 per cent silver nitrate. The silver was used in the more resistant cases. Only 11 had oral medication, 9 prontylin, and 2 Ammon. mandelate, for infection flared up or caused by treatment. In general, the patients were treated once a week until improvement was apparent, when the interval between treatment was doubled each time.

Dilatation was usually carried to 28 (French). When carried to the larger sizes, as 36, temporary incontinence resulted, and we rarely go so high now as it does not seem necessary to obtain results. The majority of the patients required three or four successive treatments to obtain relief of symptoms.

TABLE V

NO. OF PATIENTS	TREATMENTS TO OBTAIN RELIEF
7	1
11	2
17	3
12	4
6	5
3	6
4	7

*Gomenal, an ethereal oil from a plant, *Melaleuca viridiflora*, germicidal without irritating effects.

tients complaining of nocturia, only three were troubled more than once a night. This is emphasized as nocturia is not characteristic of the condition.

TABLE I

COMPLAINT	NO. GIVING COMPLAINT
Urinary frequency	64
Urgency	24
Burning	23
Nocturia	16
Pressure	13
Terminal tenesmus	6
Coughing incontinence	3
Small stream	1

The etiology of this condition is obscure. Age has no connection with it, as is seen when the cases are broken down into age groups.

TABLE II

AGE	NUMBER
21-30	20
31-40	26
41-50	18
51-60	19
61 on	16

Childbirth and the resulting relaxation of the pelvic fascia is not a factor, for 50 had children and 50 did not.

Associated gynecologic difficulties do not cause the irritable vesical neck in view of the paucity and variety shown in Table III. If cervicitis

TABLE III

Fibroid	3
Prolapse	4
Cystocele	5
Rectal polyps	1
Trichomonas vaginitis	1
Pruritus	1
Cervicitis	1

were a cause of any importance, one would expect more cases listed. Cystoceles account for the three cases of coughing incontinence. The absence of gynecologic pathology in this group of 100 cases came somewhat as a surprise, as the general impression seems to be that the etiology is in the gynecologic tract.

However, previous gynecologic treatments and surgery may be an etiologic factor. In many such cases there is retention of urine with resultant infection of varying degrees which causes irritation. Sixteen of this series had previous laparotomies; 5 had had repairs; 4 had had x-ray treatments; and 2 had had radium.

Three patients stated that intercourse aggravated or caused recurrence of the difficulty; however, two of these had hypospadias of the

The sitting posture also allows any serum or blood which may be in the vagina to be expelled. The vagina runs downward and backward and holds, as a cup, any serum or blood if the patient remains on her back. Theoretically, at least, the erect posture allows this to be evacuated, thus preventing an undesirable culture medium for bacterial growth.

The advantages of this routine are:

1. Nonabsorbable sutures permit removal of the suture, leaving no foreign bodies or knots which may cause pain or other trouble.

2. Sitz baths:

A. Reduce the possibility of infection and disruption of the wound.

B. Aid in the prevention of edema and swelling of the wound.

C. Increase patient's comfort and sense of cleanliness.

D. Are applicable in dirty or contaminated cases with vulva infection or when the wound is potentially infected.

E. Facilitate nursing care, because there is less odor and beds are less soiled.

Summarized, this means greater assurance of satisfactory healing and a more comfortable post-partum course.

Technique

After the episiotomy or the usual perineal dissection (in which the vaginal mucous membrane should be left attached to the underlying fascia), the upper point of the mucous membrane wound edge is caught with a clamp. The suture is put in about one centimeter above this point and tied loosely, as if being tied over the little finger. The mucous membrane edges are then approximated by a running quilt suture. This everts the edge of the mucous membrane and approximates a larger surface of the underlying fascia, which is really the supporting structure. This suture is carried on down and used to approximate the skin surface after the deep sutures have been put in.

The mucous membrane suture is stopped at the vaginal outlet and the deep sutures are put in. These deep sutures consist of two figure-of-eight and one single loop suture at the vaginal orifice.

The figure-of-eight sutures are put in with the deep loop for the muscle layer and the outer loop for the fascia coming out at the skin edge. They are tied with not too much tension.

The suture at the orifice of the vagina is put in in the usual manner. A large heavy needle is used; the muscles are caught well up in the labia majora, then coming back to the skin edge. Re-thread the deep end of the suture and repeat on the opposite side.

The running-quilt (or mattress) suture from the vagina is then continued down after the deep sutures are in place and tied. The edges of the skin are everted, which brings a larger fascia surface together and results in a stronger wound.

Before tying the skin suture a cork is placed in a loop, to be removed in twenty-four hours when swelling begins. If tied tightly at the time of operation, the sutures may cut into the skin and become painful.

The ends of all sutures are tied together and left long to facilitate removal. This group of suture ends is kept away from the rectum by tucking them through a loop of the suture near the vaginal outlet.

The skin is carefully avoided in placing the deep sutures, because the pressure exerted on nerve endings of skin definitely increases the pain. They are tied at the skin edge making them available for removal by clipping there.

The two patients who had polyps were treated by electrocoagulation.

Some of this series is of recent date; however, forty patients were followed over a period of nine years, and it was found that the average number of treatments a year to maintain normal function and comfort was two. It is important that these patients realize that they are only being relieved, not cured.

The results are tabulated as "good," "improved" and "not helped." The "good" group are functioning normally, while the "improved" group are not satisfactory in all particulars. Ninety-eight of the 100 were followed up.

TABLE VI

Good	75	(4 wear rings for cystocele and prolapse)
Improved	18	
Not helped	5	

In conclusion, 75 out of 100 patients with irritable vesical neck were returned to normal function by dilatation of the urethra and instillation of medication. So simple a measure should be more generally used.

561 UNIVERSITY AVENUE

PERINEAL REPAIR WITH NONABSORBABLE SUTURE AND POSTOPERATIVE SITZ BATHS

A. P. HUDGINS, M.D., CHARLESTON, W. VA.

I DESIRE to comment on the favorable results which have followed the employment of nonabsorbable suture in perineal repairs, using, in addition, as postoperative treatment, sitz baths in hypertonic salt solution. Obstetric cases were the first to be given this type of treatment and the outcome was so satisfactory that it was used in routine perineal repairs on the gynecologic service.

Patients who had received other postoperative perineal care stated that they preferred this procedure because it was more comfortable and cleaner.

The method to be discussed includes the use of (1) nonabsorbable sutures by a method which permits their easy removal, and (2) the arrangement of a sitz bath which is both comfortable and effective.

The theory prompting the trial of this method resulted from the necessity of treating contaminated perineal wounds. For example: A patient with a tear from a home delivery was brought in about two or three hours after delivery, unshaven and contaminated, for hospital repair. This is a typical illustration and the results in these cases were satisfactory.

Hypertonic salt solution was used because any serum or fluid present would be drawn out of the wound. The deep sutures protruded through at the wound edges and thus allowed the escape of serum or blood, thereby preventing edema or hematoma and minimizing the possibility of infection.

An improvement has been worked out in the mechanics of the equipment used.

A chair has been devised with a basin type seat to hold the solution. This can be moved to the patient's room. The tilt of the chair has been so arranged that the weight is kept off the painful perineum. A smaller amount of water can be used, thus assuring an adequate concentration of salt.

A heating device to maintain the desired heat of the solution has been worked out which has not been available in the other equipment. This adds to the comfort of the patient as well as the efficiency of the treatment (Fig. 3).

Coarse barrel salt (ice cream salt, rock salt) has been found to be less irritating than the more refined table salt, perhaps because of the magnesium carbonate or other chemicals added to make table salt flow more easily. In addition to the salt, vinegar (about 6 ounces) has recently been used. Karnaky claims that vaginal wounds heal more quickly in acid solutions.

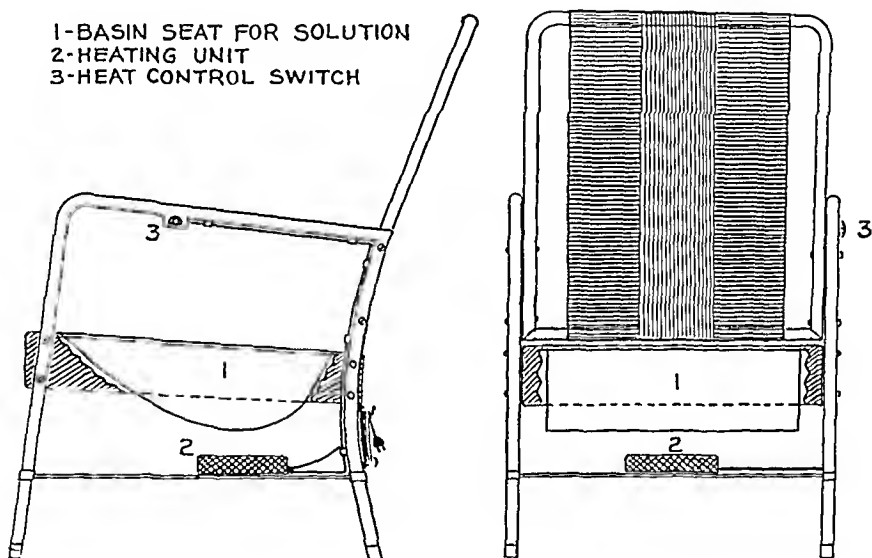


Fig. 3.—Sitz bath chair with heating device.

This type of operation with some modifications has been used on 41 obstetric and 48 gynecologic cases, which have been followed through for end results. (About 50 more cases have since been added to the series with equally good results.)

The results have been uniformly good. There was only one disruption of the perineal wound. This occurred in an obstetric case with many complications, including a temperature of 104° F. due to an acute respiratory infection preceding delivery. There was a stillborn-deformed child and an extension of the episiotomy to the rectal sphincter. The wound granulated well but did not heal by primary union. Hypertonic vaginal compresses were used instead of sitz baths in this case, due to the complicating respiratory infection and fever.

In one case a suture inadvertently was placed through the rectal mucosa and by error was allowed to remain. Some infection resulted in the perineum, but the drainage cleared up and healing was satisfactory.

The repair of the perineum is made entirely with a heavy nonabsorbable suture. It should be heavy to prevent the possibility of breaking and remaining deep in the perineum. Number 8, 10, or 12 white cotton has been found entirely satisfactory, though the other types of sutures have been used and no disadvantages found.

The sutures must be put in so that all can be removed easily and completely. Also, it has been found advantageous to allow the deep sutures to come through the skin edge thus acting as a wick.

Fig. 1.

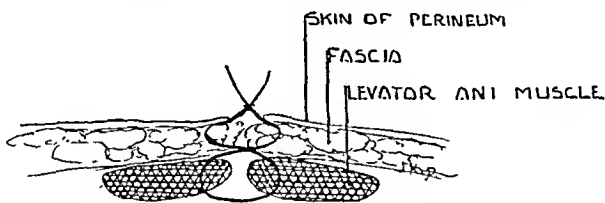
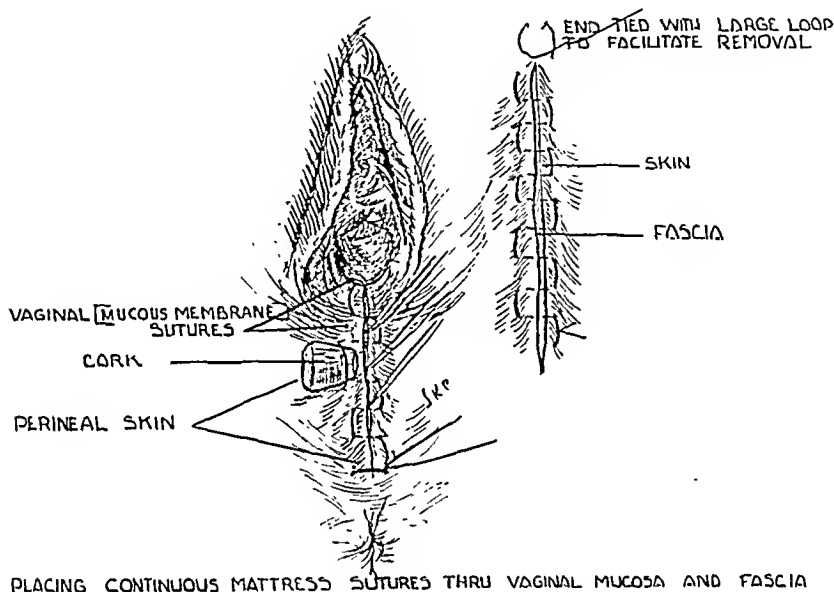


DIAGRAM SHOWING FIGURE OF EIGHT SUTURE

Fig. 2.

The sutures are usually removed the eighth day. If the skin sutures are causing discomfort they may be loosened earlier. The deep sutures, though usually removed before the patient leaves the hospital, have been left in for three weeks or more without harmful effects.

Early rising and "getting into the tub" is a mental hazard for the patient and may prove a handieap to be overcome at first. This problem disappears quickly, however, when results are observed.

The treatments were at first given in the regular bath tub. The water was limited to one or one and one-half inches and about 6 ounces of salt added. Heat was maintained by adding hot water as the solution cooled.

The movable sitz bath chairlike tub, devised for this type of treatment, makes the procedure simpler because it can then be given in the room and will not congest the bathroom facilities.

blood. Four days after transfusion there were 66,000 platelets, and bleeding time was ten minutes twenty seconds.

A second transfusion of 250 c.c. of citrated whole blood was given August 25. Three days later the gums stopped bleeding and the urine began to clear. At this time there were 76,000 platelets. Bleeding time was five minutes thirty-five seconds.

A third transfusion of 300 c.c. of citrated whole blood was given September 1, and three days later the platelet count increased to 100,000, while the bleeding time was normal.

During the stay in the hospital, the fetal heart sounds remained good at a rate of 130 to 140. The petechiae began to fade and no new petechiae formed. All gum bleeding stopped and the urine was clear of blood.

Transfusions were withheld for eight days and on September 9, the laboratory work was repeated. The platelets had fallen to 68,000 and bleeding time increased to ten minutes, thirty seconds.

At this time there appeared to be two courses of treatment: To continue frequent transfusions, or to consider splenectomy. It was believed that the baby would not be viable, and it was estimated at about three pounds. In continuing transfusions there would be the risk of transfusion reaction and little change in the course of the disease. However, in performing the splenectomy with the seven months' pregnancy, there would be the risk of labor following the operation.

A fourth transfusion of 400 c.c. of citrated whole blood was given September 9. The patient was started on corpus luteum, 2 c.c. every eight hours, and after the third dose the splenectomy was performed September 12. There was minimal bleeding at the time of the operation, and the patient was returned to her room in good condition. The fetal heart was heard for forty-eight hours after the operation. The post-operative course was uneventful. Morphine, gr. $\frac{1}{4}$, was given on two occasions after the operation with pantopon, gr. $\frac{1}{3}$, on three occasions.

No fetal heart sounds were heard after September 14. The laboratory reported 168,000 platelets and normal bleeding time on September 15.

Labor began the next day and after three hours of moderate pains the cervix was fully dilated and the patient was delivered of a stillborn, slightly macerated female child, by low forceps under gas-oxygen anesthesia. The placenta separated in four minutes and was expressed with minimal bleeding. Intravenous ergotrate was used following the third stage. The placenta was complete and normal. The infant weighed three pounds and four ounces.

The abdominal incision was examined following the delivery and was found to be intact. The skin clips were removed on the following day. There was no abnormal flow of lochia.

On September 24, twelve days after the splenectomy, there were 340,000 platelets. At the time of discharge from the hospital there was no recurrence of bleeding or petechiae.

Pathologic Report.—The spleen measured 13 by 11 by 5 cm. Sections revealed no pathology in the lymphoid follicles. The splenic pulp, however, had an increase in fibrous connective tissue stroma. There were many destroyed red blood cells and the red cells were accumulated in the various parts of the spleen.

Diagnosis: Hyperplastic spleen.

There was one case of definite puerperal infection which developed. This woman was not a good surgical risk because of poor hygienic condition, poor nutrition, and anemia. The error could quite easily have been a break in technique other than in the postoperative care.

There was one case of an unexplained elevation of temperature starting on the eleventh day after delivery. There was no evidence of localized pelvic infection found. This must, of course, be considered a puerperal infection.

The advantages of early rising after operations have been brought forth and explained on several occasions. Allowing the patient up in a chair or on the side of the bed adds much to the comfort, and according to statistics reduces the postoperative complications of a respiratory and vascular nature.

It is striking how much more quickly the patient has a normal, healthy color and appearance following this early rising, and how much more quickly they overcome the postoperative shocked appearance.

One must, of course, be convinced of the efficacy of early rising to take full advantage of the sitz bath. Hypertonic hot compresses may be used but have not been found to be as effective as the sitz bath.

THROMBOCYTOPENIC PURPURA

DAN PHYTHYON, M.D., AND ROBERT E. LARTZ, M.D., SHARON, PA.

THROMBOCYTOPENIC purpura is a rare complication of pregnancy. The following case report concerns a seven months' pregnancy in a primipara in whom symptoms and laboratory studies were typical of thrombocytopenic purpura.

B. Z., a white, married woman, 28 years of age, para 0, gravida i, was admitted to the Christian H. Buhl Hospital Aug. 19, 1942, approximately seven-months pregnant with the complaint of bleeding from the gums for four days, an increasing number of small purple spots over the extremities and back, and bloody urine for the past twelve hours.

Her last menstrual period was Jan. 8, 1942. The early pregnancy was uneventful with the exception that she bruised easily after any slight contusion. There was no family history of hemorrhagic diathesis. Her past history was uneventful except for an appendectomy two years ago.

Inspection on admission revealed a well-nourished and well-developed female. The skin of the extremities and back was covered with many small red purple spots. The head was negative except for bleeding of the gums and clots of blood at the tooth line. The abdomen was enlarged to a seven months' pregnancy; fetus was in a vertex presentation, fetal heart 130, in the L.L.Q., and height of the fundus was 25 cm.

Blood studies on admission showed a secondary anemia, leucocyte count and differential normal, coagulation time normal, bleeding time increased, a noncontracting clot, and platelet count of 68,000. These findings substantiated a diagnosis of thrombocytopenic purpura.

On the day following admission, 500 c.c. Type A citrated whole blood was transfused without reaction. The condition of the patient remained the same. Her gums continued to bleed and the urine contained free

Editorial

CAUDAL ANESTHESIA IN OBSTETRICS

ATTEMPTS to relieve the discomforts and, what are generally designated as the "pains" of labor, have constituted an ambitious project for clinical research, particularly since the middle of the last century when Sir James Simpson advocated inhalations of chloroform for this purpose. He preferred the latter to ether as more readily administered and, in his belief, less dangerous, only to meet with the extended opposition of many members of the medical profession as well as the clergy. The risks of even this comparatively simple procedure, however, came to be recognized and in 1880 Klinkowitch, of St. Petersburg, proposed that nitrous oxide be given intermittently with each "pain."

The admitted disadvantages and occasional dangers associated with most inhalation methods stimulated the introduction in 1902, by Kroenig and Gauss, of the widely heralded "twilight sleep," which depended on the combined hypnotic and amnesic effects of morphine and scopolamine. This was hailed as the *sine qua non* of satisfactory obstetric deliveries, and through the medium of the lay press generated a public demand on physicians for its universal employment. The fact that many babies were asphyxiated in greater or less degree stimulated further search for an ideal, and a succession of sedative drugs specifically directed to the relief of labor pains appeared on the medical horizon. To oral and hypodermic administration an approach through the spinal canal has been added in more recent years based on experiences in general surgery. Solutions of the cocaine derivatives have been employed for this purpose, and now the effort is to limit the field to the sacral and lumbar plexuses by continuous bathing of nerve trunks with the anesthetic through the medium of the peridural space.

It is claimed by Hingson and Edwards in a recent article* that the analgesia developed by their special technique is safe for both mother and child, and in this report they describe their observations in a large series of cases (589) conducted in various places either by themselves or under their supervision, with almost universally satisfactory results. Following this, in the same journal, is a preliminary report by two other investigators† of a much smaller series in which, however, the disadvantages and contraindications are more clearly enumerated. These should be carefully studied by those who may undertake to employ the

*J. A. M. A. 121: 225, 1942.

†Gready, T. G., and Hesseltine, H. C.: Ibid, p. 229.

Follow-Up.—Four months after operation the patient was in good health. Menses were regular every four weeks, and flow lasted five days. A blood study on Jan. 21, 1943, revealed 241,000 platelets, normal bleeding and coagulation times, 4,160,000 red blood cells and 8,500 white blood cells.

The splenectomy was performed by Dr. C. H. Moses of Sharon, Pa.

Summary

A case of thrombocytopenic purpura complicated by a seven months' pregnancy is presented. Frequent transfusions were given without evident clinical improvement. A splenectomy was performed without disturbing the pregnancy. Liberal amounts of corpus luteum were given as pre- and postoperative treatment. However, on the fourth postoperative day, the patient was delivered of a premature stillborn infant following a four-hour labor. The postoperative course was otherwise uneventful.

Ricci, G., and Balaguer, M.: *Placental Blood: Its Indications in Gynecology*, Bol. Soc. de obst. y ginec. de Buenos Aires 20: 850, 1941.

The authors treated with placental blood women who had the following ailments: 32 adnexal disturbances, 7 metropathies (3 juvenile and 4 pre-eclimacterie), 1 puerperal pyelitis, 1 essential dysmenorrhea, 2 puerperal endometritis, 2 pelvic congestions, and 5 inductions of labor.

The placental blood is collected aseptically immediately after birth and preserved in equal parts of a solution of sodium citrate 5, sodium chloride 9 and redistilled water to 1,000. Small transfusions of blood or serum, not exceeding 20 c.c. per day, are given in series of 6 to 10. Lately, serum transfusions have been preferred. The patient is kept in the clinic until the danger of posttransfusion reactions has passed.

Nearly all adnexal cases were chronic or subacute with lesion of one or both adnexa, palpable tumor, pain and menstrual disturbances. They presented two types of reaction to the transfusion: one was inconstant and of the posttransfusion type, and the other was localized in the genital apparatus. The focal reaction, which the authors regard as specific, consists of increase in local pain and size of the involved part, general ill-feeling and fever, sometimes exceeding 38° C. This reaction disappears after a few hours. The result is disappearance of pain and return of general well-being. Menstruation becomes regular, the size of the uterus decreases and the discharge and tumor disappear. In recurrence the treatment is repeated and gives good results. Rebellious cases are those which have received insufficient treatments: even in these, a series of transfusions may be an excellent procedure during the pre-operative stage. In menstrual disturbances, the possibility of ectopic pregnancy must always be eliminated before treatment is started. Treatment was ambulatory in most cases.

Results were good in the cases of metropathy, pyelitis and endometritis, but were not definite in dysmenorrhea and pelvic congestion in which a longer period of observation is necessary to allow drawing final conclusions. There were two successes and three failures for induction of labor.

J. P. GREENHILL.

Department of Reviews and Abstracts

Selected Abstracts

Gynecology—Pathologic and Hormones

Dutra, L. H.: Vaginal Cysts, *Rev. de ginec. e d'obst.* 36: 75, 1942.

The author reports a series of seven vaginal cysts in four patients. He operated upon these women and found that all the cysts were of Wolffian origin. The epithelia of the cysts varied in type. The author emphasizes that during operation bleeding is profuse, chiefly because there is no good line of cleavage between the cyst wall and the vaginal mucosa.

J. P. GREENHILL.

Borras, P. E., Alvaro, J., and D'Acquila, H.: Chorionic Villi Retained and Enclosed in the Uterine Muscle, *Bol. Soc. de obst. y ginec. de Buenos Aires* 20: 829, 1941.

The authors report four cases where villi were found within the uterine musculature. In one the villi were enclosed in the myometrium without any tumor formation, but in the other three the villi were found in uteri with interstitial, submucosal, and subserosal fibromyomas, respectively. There was a considerable interval between the last pregnancy and the appearance of menstrual disturbances in three patients (from six months to four years), showing that villi can be retained for a long time without causing disturbances or without proliferating. It might be thought that the symptoms were produced by the fibromas only and that the villi had not influenced the clinical picture. However, histologic examination showed that the Langhans cells had undergone no regression and that their protoplasm and nuclei were fully alive.

In the first patient, who was admitted quite some time before the menopause, the disturbances could hardly have been due to the fibroma; therefore, a degenerating neoplastic process was suspected, and it was only after histologic examination that the authors realized the symptoms were caused by the villi enclosed in the fibrous mass. In the second case the last pregnancy dated back seven years and the menstrual disturbances appeared gradually four years later until intervention became necessary. In the third patient, the free interval had been short but distinct. The Friedman test was negative and section of the specimen showed that the bloody nucleus in the myometrium was encapsulated and easily detached from the muscular wall. Histologically, the mass of villi was separated from the muscle by a heavy layer of fibrin, which explains the result of the Friedman test; the Langhans cells and plasmodium were regressing. The fourth patient was 40 and had had 16 pregnancies with 13 living children, the last birth having been two years previously. Menstruation had become gradually irregular and examination revealed a soft myoma of the fundus.

It seems reasonable to suppose that inclusions can occur in foci of endometriosis, but it is difficult to explain why the villi which have a naturally an invasive character,

procedure. In an accompanying editorial in the same journal, there are presented laudatory opinions by other observers but likewise the caution that its employment is limited to hospitals and to a carefully trained personnel.

Due and respectful consideration must be accorded to any reasonable proposal which has for its object the alleviation of the "pains" of labor. For women no longer regard these as necessary or inevitable accompaniments of childbirth. It is essential, however, that such measures be safe and practical, and it is by this yardstick that they should be evaluated.

It has been demonstrated that the anatomy of the sacral hiatus is subject to variations as is the capacity of the canal. Injury is likely and the fairly large doses of the anesthetic agent used are also fraught with danger because the individual susceptibility of the patient cannot readily be determined in advance. All of these facts must be carefully determined before any general adoption of the procedure can be permitted.

Enthusiasm for a new procedure is natural when this is based on favorable personal experience. Nevertheless a sense of balance and proportion must always be maintained in passing final judgment. In this instance apparently insufficient thought has been given to the fact that the invasion of the delicately constituted spinal canal is essentially a major procedure, often fraught with risk and uncertainty. The question may well be asked whether this is necessary to compensate the average, normal parturient for what in most instances are discomforts quickly forgotten and leaving little or no disturbance in their train.

The account of a labor conducted under the method advocated by Hingson and Edwards is captivating. There is, however, little stress laid on the disturbing factors which should be noted in the succeeding article by Gready and Hesselstine. Whether it can or should be applied in a routine manner in all cases, as apparently practiced by the original authors, is open to serious question. It seems unfortunate that the recent wide newspaper publicity may lead to false hopes among pregnant women as to the practicability and safety of a procedure which must be subjected to a longer period of observation by the trial-and-error method together with an impartial interpretation of results, otherwise even a few serious accidents may condemn what might prove a valuable addition to our obstetric armamentarium in selected cases. In this connection attention is directed to another contribution on the subject in the present issue of this JOURNAL.

chiefly of the myeloid elements. The degree of maturation of the myeloid cells varied. The same response was produced by each of these drugs in the peripheral blood. There was a leucocystosis and a fall in thrombocytes. There was a moderate decrease in red blood cells and hemoglobin. The authors finally conclude from their study that, when, given to dogs, large doses of the natural estrogens and estradiol produce hepatic changes indistinguishable from those produced by diethylstilbestrol.

WILLIAM BERMAN.

Miescher K., and Gasche, P.: Lingual Application of the Female Sex Hormones, *Schweiz. med. Wchnschr.* 72: 490, 1942.

The authors studied the lingual application of estradiol on the uterus of castrated albino rats. They observed that solutions of estradiol produced a reaction in the uterus which was 10 to 20 times as great as the oral application of this substance. In fact the lingual application of estradiol produced some effects which could not be obtained with oral injection. The authors point out a parallel between the lingual use of both the male and female hormones.

J. P. GREENHILL.

Freed, S. C., Eisis, W. M., and Greenhill, J. P.: The Therapeutic Efficiency of Diethylstilbestrol Esters, *J. A. M. A.* 119: 1412, 1942.

The authors propose a method for determining the potency of estrogens by using the subjective response of menopausal women. Only patients with moderate or severe symptoms including at least two to four hot flushes were used for testing. For the estrogens that were administered by injection, a technique was adopted whereby the length of the period of relief following the last of a series of injections was used as an index of the therapeutic efficiency of the estrogens. Three compounds were used: diethylstilbestrol, diethylstilbestrol dipropionate, and diethylstilbestrol dipalmitate. The minimal effective dose of the dipalmitate is 50 times greater than plain diethylstilbestrol.

It was found that the diethylstilbestrol was inferior to the dipropionate in efficiency since the period of effective relief is less. The dipropionate was effective on an average of five weeks. The dipalmitate was more effective than either of the other two, its effect lasting an average of nine to ten weeks.

The dipropionate is considerably less toxic than the free compound. The dipalmitate is practically free from toxicity.

WILLIAM BERMAN.

De Lisi, Giuseppe: Observations on Short Wave Therapy in Gynecological Infections, *Rassegna d'ost. e ginec.* 49: 463, 1940.

The author reports on the experimental use of short wave therapy in a series of 80 patients, who presented varying degrees of pelvic inflammatory disease. Thirty-one of the patients received the treatments during the ambulatory phases of their illnesses. The number of treatments, per patient, varied between 3 to 20 with an average range of 10 to 20 treatments for each course. Each treatment lasted seven to twenty-five minutes and was given either daily or upon alternate days. The patients received medical therapy in addition (vaccines, colloidal metals, and other drugs).

The author concludes that short wave therapy, as a therapeutic adjunct, is valuable. It is harmless in application, assists materially in reducing the pain and tends to cause earlier regression of acute pelvic inflammatory disease. He states that active febrile reactions and menorrhagia upon an inflammatory basis do not constitute contraindications.

CLAIR E. FOLSOME.

remain inactive for long periods. Probably the organism must acquire a predisposition to allow these tissues of fetal origin to develop in it. The diagnosis offers great difficulties and operation is always indicated because of the danger presented by retention of these remnants. The Friedman test after operation was negative in all four patients.

J. P. GREENHILL.

Bottiroli, Ernesto: Repeated Hydatidiform Mole, *Bol. Soc. de obst. y ginec. de Buenos Aires* 20: 847, 1941.

The author calls attention to the extreme rarity of this disorder; only one case is found in the Argentine literature. Extirpation of any uterus that has contained a mole is recommended by those who regard the mole as a malignant degeneration, in opposition to those who consider it a benign process. The author reports a case in a woman, aged 41 years, who had three molar pregnancies interspersed between six normal ones. The fifth, sixth, and eighth pregnancies were undoubtedly molar; the author attended to the last two and, when showing the vesicles to the patient, was informed that she had expelled exactly the same kind of material during the first. The distribution of these molar accidents between the fourth, seventh, and ninth pregnancies which were normal favors the theory of the ovular origin of the disorder. Hormone studies made during the third molar pregnancy revealed the same amounts as in normal pregnancy. With Brindeau, the author thinks that this absence of increase in hormones is due to the fact that the mole has ceased to grow and was simply in the stage of retention.

J. P. GREENHILL.

Dahl-Iversen, E., Hamburger, C., and Jorgensen, H.: Cystic Glandular Hyperplasia of the Endometrium Elucidated by Therapeutic Experiences in Patients and by Experiments on Rhesus Monkeys, *Acta. obst. et gynec. Scandinav.* 21: 215, 1942.

Therapeutic tests carried out by the authors showed that it is not practical by simulative therapy to cure cystic glandular endometrial hyperplasia in young women even with doses up to 42,000 international units of chorionic gonadotropin. This type of treatment merely produces a temporary reduction of the menses. After this there is a relapse. There appears to be no difference in substitutional therapy and stimulation treatment. In young girls the estrogens have no effect whatsoever.

Experiments revealed that chorionic gonadotropins are capable of producing physiologic changes in Rhesus monkeys but these are temporary. After treatment is discontinued, the ovaries resume their normal function.

Administration of estrogens for a sufficient length of time produces changes in the monkey that have some morphologic resemblance to cystic glandular endometrial hyperplasia in the human. However, the symptoms which appear in the human being are absent, namely, hemorrhage and necrosis.

J. P. GREENHILL.

MacBryde, Cyril M., Castrodale, Dante, Helwig, Elson B., and Bierbaum, Olga: Hepatic Changes Produced by Estrone, Estradiol, and Diethylstilbestrol, *J. A. M. A.* 118: 1278, 1942.

Dogs were used in this experiment, and they were given equal quantities of estrone, estradiol benzoate, and diethylstilbestrol dipropionate which were compared on an equal standard (international unit). The hepatic changes that occurred consisted of fatty degeneration and hydropic degeneration. Alterations in the parenchymal cells were not prominent. The bone marrow showed a variable degree of hyperplasia

prolapse. Sections of these ovaries showed changes in the follicular apparatus analogous to those found in human ovaries with cystic degeneration. (3) Partial resection and suspension of such ovaries yielded the best results.

HUGO EHRENFEST

Castro Barbosa, J.: *Simultaneous Torsion of Bilateral Dermoid Ovarian Cysts*, *Rev. méd. munic. (Rio de Janeiro)* 1: 207, 1941.

A 27-year-old woman with a normal menstrual history noted, at her last period, a decrease in amount and change in color. Eighteen days later she was taken with generalized lower abdominal pain soon followed by nausea, vomiting, and a sense of fullness in the lower abdomen. On examination there were hyperesthesia over the iliac fossae and some defensive spasm on the right. Rectal and vaginal examination revealed tenderness in both iliac fossae and on the right a mass separate from the uterus was made out. Puncture of the cul-de-sac disclosed blood and the patient was subjected to laparotomy with a diagnosis of ruptured ectopic pregnancy. Bluish congested ovarian tumors were found on both sides, each one twisted twice on its pedicle. These were removed and the patient made a normal recovery. With the appearance of menopausal symptoms, the author has announced his plans to implant an ovary of a woman of similar blood group in the patient's uterus.

R. J. WEISSMAN

MacFee, William F.: *Benign Tumors of the Ovary Associated With Ascites & Pleural Effusion*, *Ann. Surg.* 113: 549, 1941.

The author reports a case of multicocular cystadenoma of the ovary associated with ascites and pleural effusion, which constitutes an exception to the type of ovarian tumor which has ordinarily been associated with this complication. The predominant physical symptoms were related to interference with proper aeration, and the physical findings were similar to those observed in cases of ovarian fibroma with ascites and pleural effusion. Ablation of the tumor and removal of the pleural fluid likewise terminated the disease.

WILLIAM BERMAN

Heller, J.: *Floating Ovarian Cystadenoma*, *Zentralbl. f. Gynäk.* 64: 1231, 1940.

A 24-year-old virgin noted daily gradual and painless abdominal enlargement. A diagnosis of inoperable carcinoma of the liver was made in one clinic and the woman received 5 series of deep roentgen therapy, without relief. There was nothing unusual in the menstrual history. The past few months had been marked by anorexia, tachycardia, and effort dyspnea. Roentgenograms revealed only slight elevation of the diaphragm. On rectal examination a tumor was felt which appeared to fill the whole abdominal cavity. It was hard in consistency in the hepatic region and soft and fluid on the left side of the abdomen. In the genupectoral position, rectal examination revealed a small uterus forced to the left and a pedicle arising from it on the right. The abdominal fluid was emptied by trocar and a pseudomucinous cystadenoma was removed. The tumor and fluid weighed 31 kilos. The interesting feature of the case appears to be the importance of the knee-chest position in making the pedicle available to the examining finger. Previous physicians had been misled, according to the author, by the apparent location of the tumor, its displacement of the liver and the appearance of "liver spots" on the patient's skin.

R. J. WEISSMAN

Mussio-Fournier, J. C., and Albrieux, A.: The Absorption of the Sex Hormones by the Skin. (Discussion of a Case of Facial Hypertrichosis Relieved by Intradermal Injections of Folliculin), *Presse méd.* 48: 569, 1940.

The authors report that the masculine or female hormones, when applied to the skin in an ointment or in alcohol or oily solutions, are absorbed locally by the skin and produce their characteristic reactions. In a case of facial hypertrichosis locally applied folliculin produced a loss of hair while the controlled side of the face continued to evidence hypertrichosis. Three photographs are offered in the evidence submitted. It was interesting to observe that the patient, described in this report, gave a history of hypomenorrhea with periods of secondary amenorrhea preceding and during the development of the hypertrichosis.

CLAIR E. FOLSOME.

Wilkinson, R. J.: Chronic Pelvic Disease Resulting From Childbirth Improved Operative Technic, *South. Surgeon* 11: 359, 1942.

The author was impressed with the large number of patients with pelvic complaints who attributed their symptoms to antecedent childbirth. In a series of 246 such patients with chronic pelvic disease uncomplicated by associated tubal abnormalities, fibroid tumors, ovarian cysts or procidentia, there was no response to office treatment, and surgical corrective procedures were employed. The usual complaints were vaginal discharge, backache, disturbed menstrual function, lower abdominal pain and nervousness; the common pelvic findings were an enlarged, retroverted uterus, broad ligament varicosities, endocervicitis, and perineal lacerations. All of these patients had a vaginal repair and cervical dilatation and conization, and, in 242 subtotal hysterectomy with ligament shortening was performed. No fatalities occurred. There were 167 replies to a questionnaire sent two to four years after operation. Ninety-three per cent felt that the surgical repair was beneficial; 56 per cent were still menstruating, and the members of this group obtained the greatest relief from all symptoms. The observation that relatively few patients in whom some of the endometrium was retained require estrogen therapy, impressed the author with the importance of performing defundation, and it strengthened his belief that there is a uterine hormone.

Careful postnatal check-up examinations with early institution of corrective treatment will prevent the development of more extensive pelvic abnormalities. Later, conization of the cervix and vaginoperineal repair may be all that is required. When more extensive changes have occurred, the additional performance of defundation with ligament shortening is advocated. For the patient 40 years of age or older, panhysterectomy is the procedure of choice.

ARNOLD GOLDBERGER.

Ovarian Neoplasms

Weed, John C., and Collins, Conrad G.: Cystic Degeneration of the Ovaries, *Surgery* 11: 292, 1942.

On the basis of extensive experiments on animals the writers arrive at the following conclusions: (1) Cystic degeneration of the ovaries, formerly thought to be the result of chronic infection, is now variously ascribed to sympathetic dysfunction and hormonal imbalance. Circulatory impairment is an infrequently considered but important etiologic factor. (2) Circulatory impairment was produced in the ovaries of 18 rabbits and one dog by either vascular ligation or artificial

In a description of the embryology, it is pointed out that the anlage of the adrenal cortex develops at about four weeks, whereas the medulla does not appear until at least four weeks later. This apparently explains the frequency with which portions of the cortex reach the pelvis in association with the development of the internal genitals. An extremely small proportion of these develop tumors while most disappear with advancing age.

The tumor cells are characteristically those of the adrenal cortex. Three histologic forms are recognized in the tumor:

1. Closely placed parallel strands of cells.
2. Solid masses separated by connective tissue.
3. Occasional adenomatous, papillary, or cystic forms are reported.

The histology is characterized as well by marked vascularity, hemorrhages and necrosis.

It is a peculiarity of the tumor that it often, though not always, changes the sexual orientation of the host bringing about demasculinization of the male and defeminization of the female. The author believes that this is more likely than that sex reversal occurs. A hypothetical explanation of this loss of sex specificity is discussed. The author summarizes the 16 reported cases and adds two of his own.

J. L. McKELVEY

Sammartino, R., and Herrera, R. G.: Myeloid Tumor of the Ovaries, Rev. méd. Latino-am. 25: 284, 1939.

This is an unusual case because of the lack of symptoms referable to the disease and because the primary focus apparently was in the ovaries. A 35-year-old housewife, dying after an operation for a tumor of the cerebellopontine angle, was autopsied with the postoperative diagnosis of corticocerebeller arachnoiditis. The findings were negative except with respect to the myeloidosis. The uterus was small and atrophic with a few fibrous perimetrial adhesions. The ovaries were enlarged, ellipsoid, one measuring 8 by 5 by 3 cm., the other 7 by 5 by 4 cm. There were similar on section, the cut surface resembling a sectioned lymphatic gland. Medullary nodules were apparent, with a fascicular connective tissue. A few old corpora lutea and a condensed ovarian stroma were found at the hilus. The serous surfaces were pale, having a few superficial adhesions and a few cystic follicles. Microscopically the granulocytic series was well represented, with an abundance of eosinophiles. The pre-erythrocyte series was present in lesser proportion. A few microscopic foci were found in the kidneys and pancreas. There was a questionable infiltration of the meninges.

R. J. WEISSMAN

Traut, Herbert F., and Marchetti, Andrew A.: A Consideration of So-Called "Granulosa" and "Theca" Cell Tumors of the Ovary, Surg., Gynec. & Obst. 70: 632, 1940.

The Society of Gynecological Pathologists of New York has collected a group of 61 ovarian tumors which have been diagnosed as belonging to the group of neoplasms having their origin in the theca granulosa cell complex. The authors were appointed to study these tumors as well as the clinical data of the patients from whom they originated. The work is as yet incomplete; however, the material was found to yield information justifying a partial report at this time, with the following conclusions:

The use of Foot's silver stain makes possible the differentiation of theca from granulosa cells in most instances.

Kny, Walter: Arrhenoblastoma, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 406, 1940.

Robert Meyer's classification of arrhenoblastomas is briefly reviewed. A case is described which belongs to the third type, the atypical, mostly solid form. The patient was a 66-year-old para vi. Menses were normal to menopause at the age of 50. She was admitted with the complaints of dyspnea, diarrhea for some months, swollen legs, and weakness. There had been increasing loss of hair from the head and a parallel growth of a beard. Clinical examination showed scanty head hair, a male beard, and no striking voice changes. Blood showed an anemia with attempts at new blood formation. The patient died seven days after admission.

Autopsy showed male distribution of pubic hair, considerable enlargement of the clitoris and striking atrophy of the breasts. The right ovary contained a firm elastic tumor 8 to 10 cm. in diameter, and the left, a similar tumor about 5 to 6 cm. in diameter. The uterus and tubes were markedly atrophic. Metastases were found in the lungs, thyroid, and widely disseminated in bones.

The ovarian tumors were made up for the most part of masses of spindle cell sarcomalike tissue. Toward the periphery, epithelial strands were found. The original description should be consulted for details of tissue variations.

The various theories of the origin of arrhenoblastoma are discussed.

J. L. MCKELVEY

Hohage, Erich: Report of a Case of Disgerminoma of the Ovary, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 401, 1940.

A tumor of the right ovary, the size of a man's head, was removed from a 17-year-old girl. She had never menstruated. She showed a somewhat hypertrophic clitoris, a male type of voice, heavy bone structure, and a light beard. Otherwise, she seemed to have female characteristics. The uterus and both tubes were markedly hypoplastic. The left ovary was the size of an almond and cystic. The urine contained only follicle-stimulating hormone.

Operation disclosed a tumor which is described as a characteristic disgerminoma. X-ray therapy was given, but in spite of this metastases developed in the lungs, liver, lymph nodes, and vertebrae. The patient died five months after operation.

J. L. MCKELVEY

Kazancigil, Laqueur, and Ladewig: Papillo-Endothelioma Ovarii, *Am. J. Cancer* 40: 199, 1940.

The writers describe in detail the careful study of three malignant ovarian tumors which presented the same general picture of Schiller's "mesonephroma ovarii."

Their study, however, including a plastic reconstruction of one of these growths, failed to reveal evidence of a derivation from remnants of the primitive mesonephros. In view of the endotheliomatous character of the cells and the presence of angiomatous and angioendotheliomatous structures, they believe that these tumors are rather to be regarded as angioendotheliomatous neoplasms. The occurrence of accessory organ-specific components in two of the cases suggests an origin in a gonadal anlage. For this reason they propose for this group of ovarian tumors the name "papilloendothelioma."

HUGO EHRENFEST

Kleine, H. O.: Primary Ovarian Blastomas of the Adrenal Cortex Type, *Zentralbl. f. Gynäk.* 63: 2249, 1939.

This is a brief summary of the present status of the knowledge of pelvic hypernephromas. The author points out that the tumor is seldom if ever primarily in the ovary so that the title is not accurate.

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Thursday, May 20, through Tuesday, May 25, 1943. The Hotel Schenley in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1943.

The Pittsburgh Obstetrical and Gynecological Society will hold an informal subscription dinner meeting at the Hotel Schenley, on Saturday evening, May 22, 1943, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary of the Society, at 121 University Place, Pittsburgh, Pa. An interesting program is being provided.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1944 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

So-called granulosa cell tumors contain varying amounts of theca cell elements as well, so that pure granulosa cell tumors are rare. Most tumors contain from one-fourth to one-third of their differentiated cells in the form of theca cells. A number of tumors were encountered which had equal representations of the two cell types, while most so-called theca cell tumors also contained granulosa elements in considerable representation. One pure granulosa cell tumor and four pure theca cell tumors are described.

An attempt is made to outline the life cycle of these tumors and its relationship to the clinical syndrome they present.

WILLIAM C. HENSKE

Sailor, Seaton: Ovarian Dysgerminoma, *Am. J. Cancer* 38: 473, 1940.

A malignant tumor of the ovary histologically similar to the testicular seminoma was originally identified by Robert Meyer as arising from indifferentiated sex cells of primitive mesenchyme. He named it dysgerminoma and emphasized its tendency to occur in young women and to its frequent association with hermaphroditic or pseudohermaphroditic states. A total of approximately 160 cases have so far been reported. This new growth most frequently occurs in the right ovary of women below the age of twenty.

The author reports five new cases: (1) A 10-year-old colored girl. A large left-sided dysgerminoma was removed; later deep x-ray therapy. About thirteen months later second laparotomy for large metastases in uterus, right tube, and ovary. Died seven months later. (2) A white girl, 18 years old. A firm, fixed large tumor removed from right side. Patient in excellent condition eight months after operation. (3) A white girl, 15 years old. Firm, semisolid tumor of right ovary removed. Patient, three years after operation, still in excellent health. (4) Colored girl of 17 years. Soft, oval tumor of right ovary removed. Six years later patient perfectly well. (5) White woman, 21 years old. Large firm tumor of right ovary extirpated. Patient in good health four years later, after delivery of her second child since operation was done.

HUGO EHRENFEST

Duran, Alfredo: Cystic Teratoma Infected by *Eberthella Typhi*, *Bol. Soc. chilena de obst. y ginec.* 4: 415, 1939.

A 16-year-old girl, convalescing from an attack of typhoid fever several months previously, complained of severe intermittent pains in the right iliac fossa which became worse on lying down. She had dysuria, low-grade fever, and general malaise. At the menarche, at age of 15, there was a profuse flow of eight days' duration followed by a year of amenorrhea. Then scanty menses appeared every twenty-six days. During the two months of her illness the periods were ten and fifteen days long, respectively, the subsequent and last period being six days long.

A round tumor was palpable in the hypogastrium, occupying most of both iliac fossae and extending upward to the umbilical level. To confirm the previous diagnosis of typhoid, a Widal was done and found positive. After 26 febrile hospital days with no improvement, the patient was prepared for operation. Laparotomy revealed a pyriform cystic tumor of the left ovary, the superior pole adherent to the omentum, the inferior thoroughly adherent in the cul-de-sac of Douglas. When opened the tumor contained 1,500 c.c. of purulent fluid, from which the typhoid bacillus was cultured. Recovery was uneventful.

R. J. WEISSMAN

- Pacific Coast Obstetrical and Gynecological Society.** *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting undecided, probably San Francisco, Calif., November 5-6, 1943.
- Washington Gynecological Society.** *President*, John Warner. *Secretary*, L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Norman F. Miller. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** *President*, Ralph Hoffman. *Secretary*, Purvis L. Martin, 2001 Fourth Ave., San Diego, Cal. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** *President*, J. H. Fjelda. *Secretary*, Ralph E. Leigh, 111 North Fifth St., Grand Forks, N. D.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting. (Cancelled.)
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, September, 1943, Hot Springs, Va.
- Central Association of Obstetricians and Gynecologists. *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. (Cancelled.)
- South Atlantic Association of Obstetricians and Gynecologists. *President*, Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Next meeting. (Cancelled.)
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting. (Cancelled.)
- New York Obstetrical Society. *President*, Henry T. Burns, *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. *President*, John C. Hirst. *Secretary*, James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. *President*, Edward Allen. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. *President*, Samuel Lubin. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. *President*, Lawrence Warton. *Secretary-Treasurer*, John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society. *President*, Edward Friedman. *Secretary*, Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. *President*, J. L. Gilmore. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. *President*, Frank A. Pemberton. *Secretary*, A. F. G. Egelow, 31 Maple Street, Springfield, Mass. Meetings held in May and December.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.



Reuben Peterson
1862-1942

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He was beloved by all the medical students. His lectures were always interesting, well delivered and well organized, and sprinkled with many of the anecdotes for which he was so famous.

He received abundant recognition for his professional accomplishments. He was secretary and also chairman of the Section on Obstetrics and Gynecology and Abdominal Surgery of the American Medical Association, a founder of the American College of Surgeons, and was certified by the American Board of Obstetrics and Gynecology. In 1897 he was elected to membership in the American Gynecological Society and served as its President in 1911. He was a member of the Advisory Editorial Board of the *American Journal of Obstetrics and Gynecology* from the year of its founding until he retired from professional work. During this period he maintained a constant interest in the publication and nominated his successor at the University of Michigan, Dr. Norman Miller, to take his place on the Board. He was a member of numerous medical societies. During World War I he was a Major in the Medical Corps of the United States Army and had charge of medical recruiting in Michigan. In 1936 the University of Michigan granted him the honorary degree of Doctor of Science.

In 1889, immediately after graduation in medicine, Dr. Peterson married Miss Josephine Davis. Four children were born to them.

His was a rich life, full of accomplishments, and well lived. His memory will be a constant inspiration. We, his associates, with his many friends, will miss him.

George Kamperman.

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IN MEMORIAM

REUBEN PETERSON

1862-1942

REUBEN PETERSON died at Duxbury, Massachusetts, on November 25, 1942, at the age of eighty. His death came rather unexpectedly after an illness of two months.

He was a direct descendant of George Soule, one of the Mayflower Pilgrims. He was educated at Harvard University, and after receiving his medical degree in 1889 he practiced in Grand Rapids, Michigan, for eight years. From 1898 to 1901 he was Professor of Gynecology at the Post Graduate Medical School of Chicago, and Assistant Professor of Obstetrics and Gynecology at Rush Medical School.

His period of service at the University of Michigan as Head of Obstetrics and Gynecology lasted thirty years, 1901 to 1931. It was here that he became famous as a teacher and developed the department into an excellent University Teaching Clinic. His proudest accomplishment was the organization of a system for the training of assistants. Strange indeed, in so doing he encountered actual opposition and criticism from heads of other departments. He was proud to have one of his own trained associates succeed him upon his retirement.

Dr. Peterson was chiefly a clinician. This no doubt was due to the period in which he studied and practiced. As laboratory methods developed he always eagerly embraced each new idea. But to him the laboratory was always an adjunct to his clinical work. He believed obstetrics and gynecology were inseparable and he taught and practiced both. He made many contributions to literature. The *Index Medicus* and the *Cumulative Index* recorded 219.

Dr. Peterson was greatly respected by his associates for the brilliancy of his work, his masterful ability to organize, and for his clear-cut teaching clinics. He was deeply loved for his homely virtues. Simplicity, honesty, kindness, and generosity were his outstanding traits.

Selection of Cases

The first problem to be faced was how far one could go in extending the indications for this operation. In the first three years I attempted it in eight Group III cases with extension of the disease to the pelvic wall. Three of these women died postoperatively, and I decided that this demonstrated a definite contraindication. These cases have not been included in the present series. On the other hand, I have also considered the question of Group I cases. In the past five years I have done this operation in five patients with extensive cervical involvement, but in whom the question of parametrial involvement was open to debate. In these cases there was usually some good reason why a Wertheim operation would have meant a considerable added operative risk. I still believe that the Wertheim operation with gland removal is the best procedure in the majority of early Group I cases. For persons untrained in the technique of the radical hysterectomy, I believe it safer and better to do the lymph gland operation with radiation of the cervix rather than an extensive Wertheim procedure. I can say without hesitation that iliac lymphadenectomy is a much easier and safer operation. Naturally certain fundamentals must be learned as in any surgical procedure.

From 1930 to 1935, my service at The Barnard Free Skin and Cancer Hospital, where all but eight of these operations were done, was shared with the late George Gellhorn. Since he in his six months' service used only radiation in the treatment of these Group II cases, and since the radiation technique was the same in my six months' service, this circumstance provided the ideal control for the value of the additional lymphadenectomy operations, as will subsequently be demonstrated. Since 1936, the service has been continuously in my charge, and during this time about 75 per cent of Group II cases have been subjected to the combined lymph gland and radiation treatment. Naturally certain cases were found not suited to operative procedures. Most numerous were those whose adiposity made abdominal intervention an added risk. Advanced years and debility were another contraindication. Diabetes, heart disease, nephritis, and persistent leucopenia were listed among the reasons for advising against surgical intervention. Younger individuals were given preference. Eleven were between 21 and 29 years of age, and the average age of the gland operation cases was several years lower than that of those not subjected to surgery.

Outline of Treatment

In the first three years very little, if any, preliminary deep x-ray therapy was given. The treatment with radium was synchronous with the operation. Taking advantage of the open abdomen, six to eight radon seeds were implanted in the sacrouterine and broad ligament area, totaling about 1,200 mc.hr. From below after closing the abdomen, radium capsules were applied in the usual manner. Two postoperative

Original Communications

ILIAC LYMPHADENECTOMY FOR GROUP II CANCER OF THE CERVIX*

Technique and Five-Year Results in 175 Cases

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

(From the Barnard Free Skin and Cancer Hospital)

THE logic of removing the important tributary lymph glands in cancer of the uterine cervix lies in the fact that radiation therapy, which is effective in eradicating the primary site of certain forms of cancer, fails except in few cases permanently to destroy cancer metastases in the lymph glands. In cancer of the breast, the oral cavity, the vulva, and the penis, lymph gland resections have for a long time been accepted as the standard treatment, associated with surgical ablation or radiation of the primary tumor. In cervix cancer, gland removal was for many years considered an essential feature of the radical Wertheim hysterectomy. The high primary operative mortality of this extensive procedure led many to abandon the gland resection and at present only a few surgeons, like Bonney in London, still adhere to this plan of treatment. Furthermore it is applicable only to the relatively small number of Group I (League of Nations Classification) cancers of the cervix. Group II cases, in which there is involvement of the parametrium or upper third of the vagina, without extension to the pelvic wall, are at least two to three times as numerous as the Group I cases. It was in this group that it seemed to me possible to obtain better results by combining lymphadenectomy with radiation of the primary tumor.

In 1930, Leveuf in France, and I independently conceived the possibility of this method of attack. Unfortunately Leveuf carried out this procedure in only a few cases. His report was on only three altogether. My first case done in October of that year with a large metastatic hypogastric gland is still free of recurrence. From that time up to October, 1942, my associates and I have done 175 iliac lymphadenectomy operations. Seventy of these were done over five years ago. The low primary mortality and the relatively high survival rate in the five-year cases have convinced me that the addition of iliac lymphadenectomy to the thorough radiation of the primary tumor in Group II cancer of the cervix is of definite value.

*Presented, in modified form, at a meeting of the San Francisco Gynecological Society, March 12, 1941.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

bifurcation. Lying as a rule over the origin of the external iliac vessels but occasionally pocketed in the bifurcation itself was the hypogastric gland (Fig. 2). This gland lay in a thin fibrous and fatty network. By means of a blunt-pointed forceps or seissors, it could be separated from the large vessels without trouble. Two or three small nutrient vessels were caught and ligated. Not infrequently there were two such hypogastric glands.

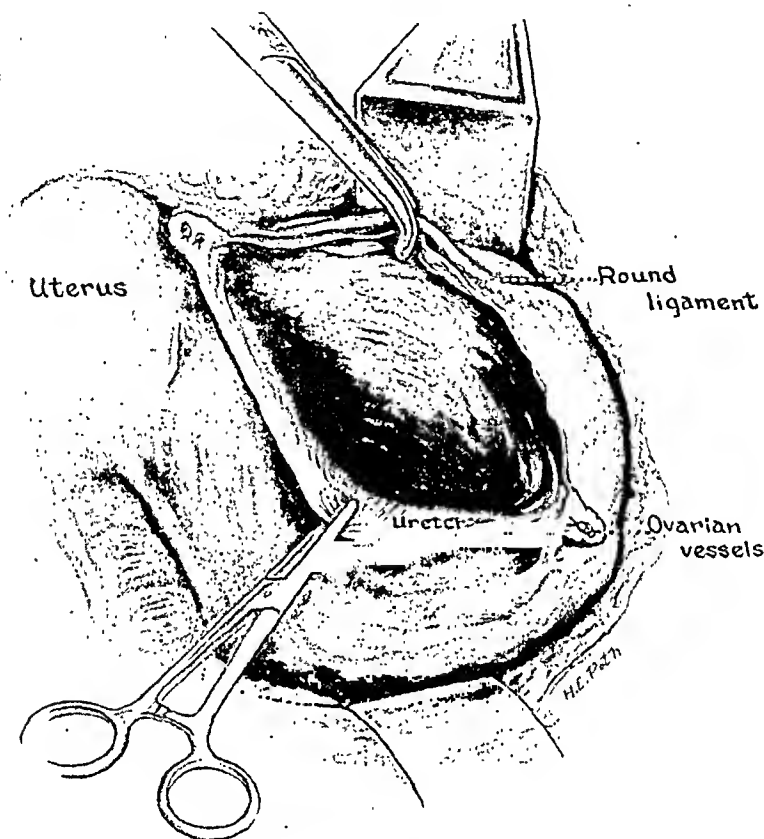


Fig. 1.—Iliac lymphadenectomy. After removal of the tube and ovary forceps are applied to the round ligament and posterior peritoneal sheath of the broad ligament and the tissues of the broad ligament exposed. The ureter is seen clinging to the posterior sheath.

The next step was exposure and removal of the obturator glands with surrounding fat (Fig. 3). These glands were pocketed beneath the external iliac vein, running parallel to it and clinging to the pelvic wall. To reach them the tissues of the broad ligament had to be opened more widely. This exposed first the obliterated hypogastric artery, rising from the internal iliac artery. The obturator gland, or glands, could usually be felt and by gently pinching between the index and middle fingers could be freed from surrounding fibrous strands so that the tissue could be caught by a forceps. Since the obturator nerve runs directly through the mass of fat and glandular tissue, the exposed tissues were grasped lightly and lifted upward, thus exposing the glistening white band of the obturator nerve beneath. The obturator chain of glands was then dissected free and nutrient vessels caught and ligated. One long thin obturator gland was almost invariably found running to the

deaths occurring in these years were in my opinion attributable to this conjunction of radium treatment with operation. One was due to embolus following radon seed implantation close to the uterine vein; the other was caused by peritonitis following the perforation of a radium capsule into the broad ligament. For this reason, since 1935, the operation has always been made a separate procedure. Previous to this time, radium was given 21 times with operation, 9 times before operation, and 6 times after operation. In the patients operated upon since January, 1936, radium was given 26 times before operation, and 113 times after operation. The absence of uniformity in this program was due partly to difficulties of hospitalization in our overcrowded institution, and partly to the fact that a number of patients had previously received radium treatment elsewhere.

The preferred plan of procedure at present is to have patients begin a course of x-ray therapy four times a week for about four to five weeks through six portals, two anterior, two posterior, and two perineal. The average x-ray dosage has been increased in the past twelve years as follows: Cases 1 to 35, 800 r. skin dose; Cases 36 to 70, 3,730 r. skin dose; Cases 71 to 105, 6,040 r. skin dose; Cases 106 to 140, 8,900 r. skin dose; Cases 141 to 175, 11,000 r. skin dose (2,500 to 3,000 r. tumor dose). The midline area where the operative incision was to be made, was protected and in no case was there necrosis of the operative wound suggesting x-ray damage. At the conclusion of the four to five weeks' x-ray treatment, the patient was again examined to make a final check on the question of lymphadenectomy. An appointment was then made for admission to the hospital two weeks later for operation. Unless there had been serious postoperative wound infection or phlebitis, the radium treatment was given eleven to fourteen days following operation, so that the patient's hospitalization did not exceed two to three weeks. The radium treatment averaged 4,500 mg. hours in the earlier period, but recently has been increased to 5,000 or 6,000 mg.hr. Originally radium was applied from two or three points, often concentrating large dosages in the cervix with increased tendency to necrosis and hemorrhage. In the last six years the application has been from five to six points (corpus, cervix canal, against cervix, vaginal fornices), using a total of 125 to 135 mg. in $\frac{1}{2}$ mm. platinum for forty to forty-five hours. My associate, Dr. A. N. Arneson, has had charge of these applications.

Operative Technique

Spinal anesthesia was employed in almost every case unless contraindicated by high blood pressure. It was frequently supplemented in longer operations by the administration of drop ether in small amounts. The intestinal relaxation produced by spinal anesthesia was helpful in getting the good exposure of the deep pelvic structures necessary in this operation. The first step of the operation consisted in the removal of the tube and ovary. Then a forceps caught the round ligament $1\frac{1}{2}$ inches from the uterus and another clamped the posterior sheath of the broad ligament (Fig. 1). Two fingers separated the peritoneal layers and exposed the structures in the iliac triangle. In all but three cases the ureter lay adherent to the posterior sheath, easily recognized as it crossed the pelvic brim. The external iliac artery and vein could readily be exposed by pressure with a gauze sponge. The internal iliac artery and vein were more deeply situated and visible only at the point of

Closure of the operative wound in the broad ligament is effected by suturing the round ligament to the sacrouterine ligament at a point approximately $1\frac{1}{2}$ inches lateral to the uterus (Fig. 5). This suture serves to obliterate the dead space in the broad ligament and prevent the collection of blood and serum in this area. Peritonization of the remaining wound is accomplished by a running stitch. A similar gland removal is then done on the other side and the abdominal incision closed in the usual manner without drainage. The operation takes approximately one and one-fourth to one and one-half hours and is not attended by any

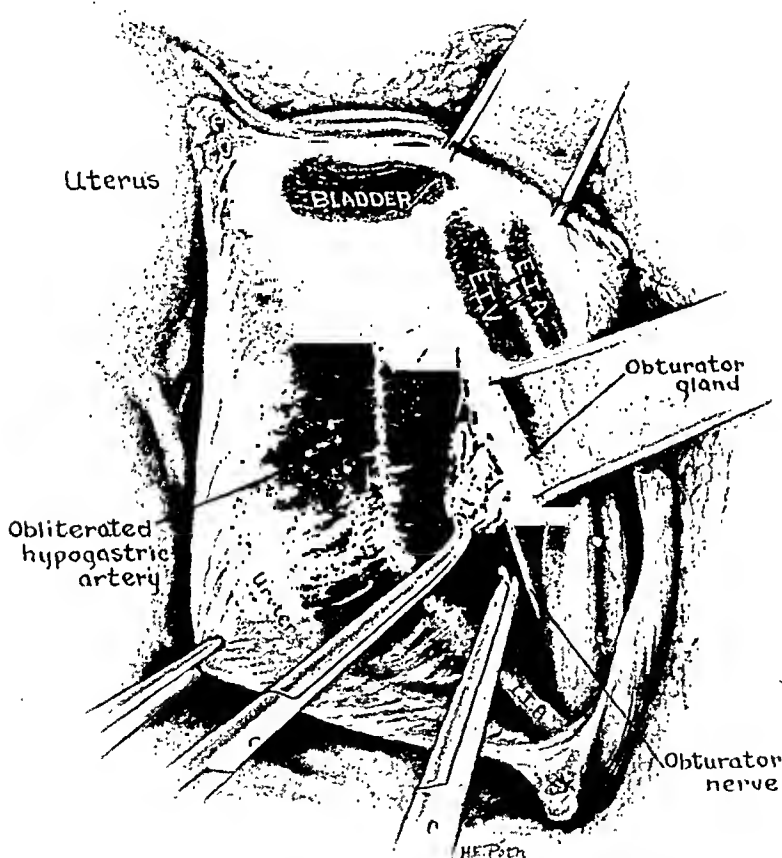


Fig. 3.—Iliac lymphadenectomy. After removing the hypogastric glands, the tissues beneath the external iliac vein close to the pelvic bone are freed and at this point the *obturator* lymph glands are noted. These glands are lifted away from the obturator nerve, clamped off and excised. One elongated gland is usually found running beneath the external iliac vein toward the obturator foramen.

shock unless hemorrhage has occurred. Postoperative morbidity is unusual. It consists of occasional minor wound infections and in four instances a low-grade pelvic or femoral phlebitis. In one case an iritis was associated with and was possibly the result of such a phlebitis. It produced no permanent damage to the eye.

Most gratifying was the low primary operative mortality. In Case 4 and Case 34, the deaths could with great probability be largely attributed to the associated radium treatment. The next operative death, due to infection, did not occur until Case 142, leaving a lapse of 107 cases without a mortality. In the total of 175 patients operated upon up to October, 1942, there were therefore only 3 deaths, a primary operative

femoral ring. At this stage of the operation, the lateral half of the broad ligament was completely denuded of lymph glands, fat and fibrous tissue exposing what I have called the *three white lines*: (1) the ureter, (2) the obliterated hypogastric artery; (3) the obturator nerve.

Removal of the external iliac glands is relatively easy (Fig. 4). They lie over the external iliac vessels near the point of exit of these vessels from the abdomen. Metastases have been so rarely found in these glands that in cases where there have been technical difficulties in removing the hypogastric and obturator glands, it has not always been deemed

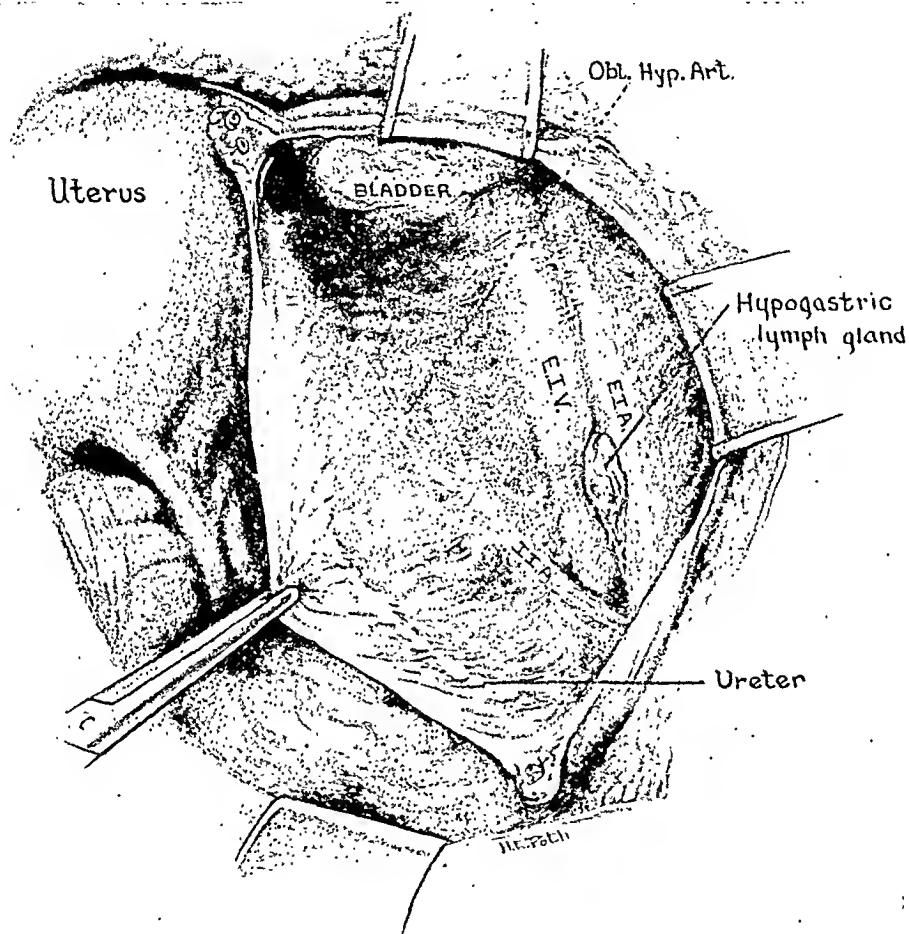


Fig. 2.—Iliac lymphadenectomy. Deeper exposure of the tissues in the lateral portion of the broad ligament reveals the external iliac artery (E.I.A.) and vein (E.I.V.) and the internal iliac artery (I.I.A.). Near the bifurcation of the arteries can be seen loose connective tissue containing one or more *hypogastric* lymph glands.

advisable to prolong the operation by this added procedure. In a limited group of cases, palpation of the point of crossing of the ureter and the uterine vessels revealed a small hard ureteral gland. If no such gland could be palpated, this area was not widely opened up. Where such a palpable ureteral gland was found, the uterine vessels were doubly ligated and the gland removed after following the ureter to this point. Routine ligation of the uterine vessels as suggested by Duncan was done in three cases, but it was felt that this might predispose to necrosis of the cervix when radium was subsequently applied, and hence has not been adopted as a part of the operative technique.

mortality of only 1.72 per cent, and in the last 140 cases, a mortality of 0.7 per cent. The dissections in the last seven years have been far more extensive and the number of lymph glands removed almost twice as great as in the first five years, and yet the operative mortality has been less than 1 per cent. Certainly no one can any longer maintain that this procedure is not justified because of its surgical risk.

Technical Difficulties

Since some of these lymph glands are only 1 to 2 mm. in diameter, it is at times no easy matter to locate them. This is particularly true of the important hypogastric glands. At times the most careful palpation after opening the leaves of the broad ligament reveals nothing. The gland may lie not in the iliac triangle but lateral to the external iliac

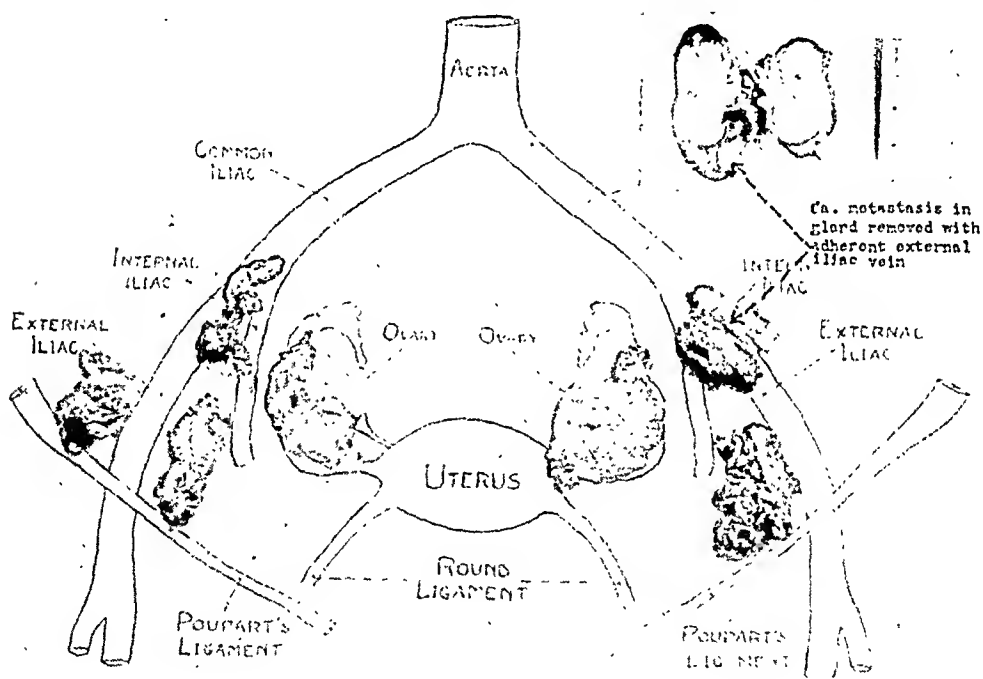


Fig. 6.—Photograph of lymph glands removed by operation, placed on a phantom showing anatomic distribution. In this case the left hypogastric gland was cancerous and densely adherent to the external iliac vein, requiring resection of the vein. Section of this gland and vein seen in the upper right corner.

artery between it and the psoas muscle. Careful dissection of the entire fibrous fatty sheath over the large vessels will usually disclose one or two small glands. In fact the larger glands are more easily removable. Size of the gland is no sure index of metastases. The large ones often show no cancer, while the small ones may contain them. The obturator and external iliac glands are uniformly larger and their anatomic distribution more constant.

A serious operative difficulty is extensive adhesions to the external iliac vessels. Heavy preoperative radiation predisposes to such adhesions, often associated with cancerous invasion of the lymph gland. In three of my earlier cases the extensive firm adhesion of such a gland to the external iliac vein made me desist from its removal, but since I have

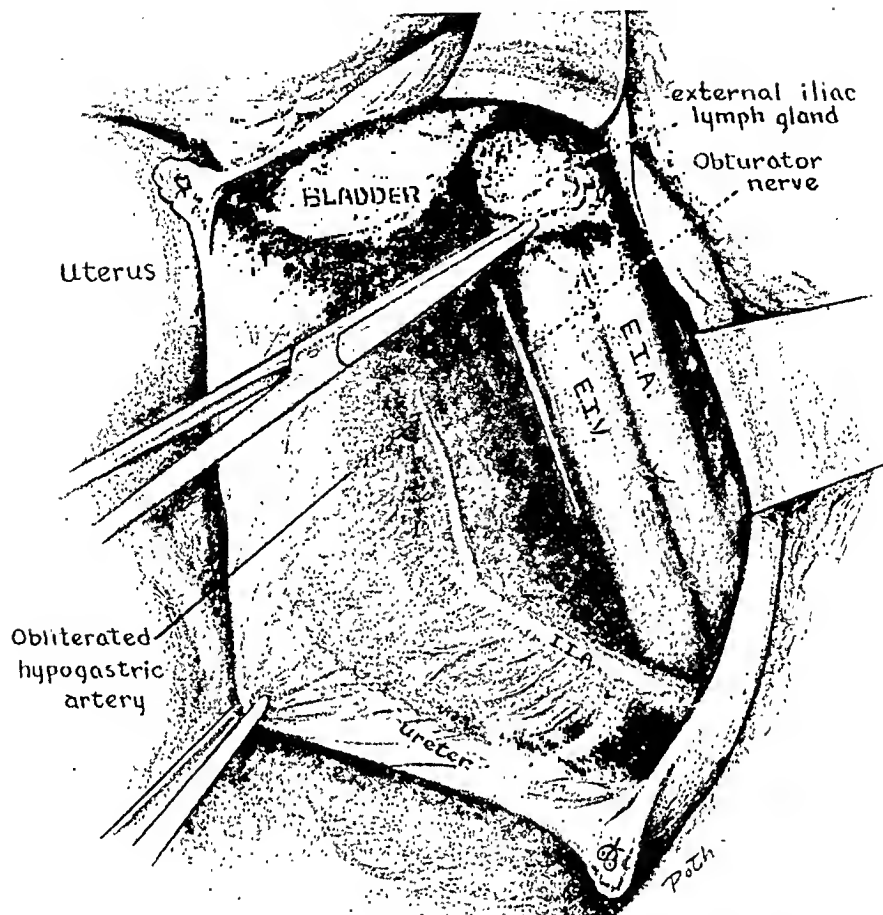


Fig. 4.—Iliac lymphadenectomy. At this point three white bands are seen crossing the base of the open space: (1) the ureter; (2) the obliterated hypogastric artery; (3) the obturator nerve. Now the external iliac glands are detached from their site near the inguinal ring and excised.

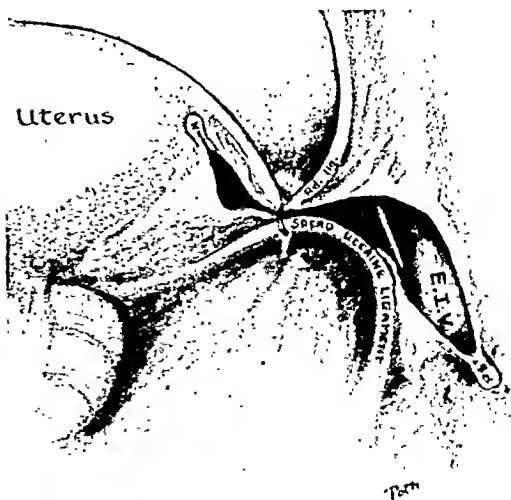
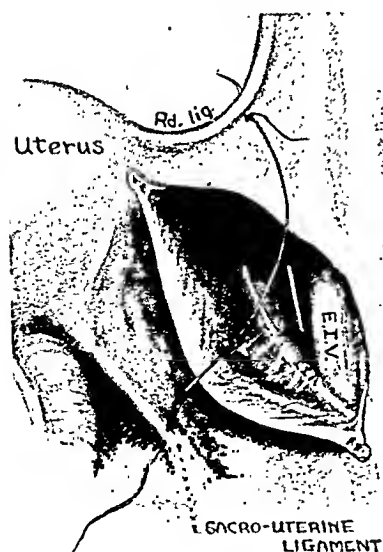


Fig. 5.—Iliac lymphadenectomy. Occasionally a small ureteral gland is found near the crossing of ureter and uterine vessels and removed. Closure of the dead space in the broad ligament is accomplished by suturing the round ligament to the sacro-uterine ligament at a distance of about one and one-half inches from the uterus.

Most numerous were the cases of adnexal disease. These consisted of chronic salpingitis, hydrosalpinx, cystic ovaries and endometrial cysts of the ovary. Myomas of the uterus were encountered 14 times. In eight women the tumors were so large as to make myomectomy or a supravaginal hysterectomy indicated for technical reasons. In one patient a huge ovarian cyst reaching to the edge of the ribs had to be removed before the lymphadenectomy could be done.

Of special interest were two cases of pregnancy complicating the cervix carcinoma. One patient was three months pregnant and aborted following the radium treatment which in this case preceded the lymphadenectomy. The other was a woman with a Group II cervix cancer who was pregnant about twenty-seven weeks. She was given no preoperative radiation. A cesarean section was done and a living but premature child obtained, which, however, died six hours later. The section was followed by a high Porro hysterectomy and a double-sided lymphadenectomy. X-ray treatment was begun two days after operation, and at its completion four weeks later radium was applied from below. This patient died of a local recurrence eighteen months later.

Glandular Involvement

In every case, each special group of glands was placed in a separate bottle and duly labeled (hypogastric, obturator, external iliac, ureteral, right or left) so that the exact points of metastasis could be distinguished. A total of 1,137 glands were removed, an average of 6.5 glands per case. In order of frequency, cancer was found in the: (1) hypogastric, (2) obturator, (3) ureteral, and (4) external iliac gland. When metastasis was present, more than one gland was often involved. Metastases were sometimes bilateral. Of the 175 cases studied in this way, 47 showed evidence of carcinoma in the removed lymph glands. This incidence of 26.8 per cent is lower than that shown in earlier reports (33 per cent in 1936). Apparently this was due to the prolonged and heavy x-radiation patients have received preoperatively in recent years. The marked disintegration of lymph follicles and the extensive replacement of lymphocytes by fibrinous hyaline and fatty tissue in those glands that were thus heavily radiated bears testimony to the destructive effect of the x-rays. Experience in the treatment of other cancers with deep x-ray therapy would lead one to believe, however, that cancer metastases may frequently be rendered unrecognizable but not wholly destroyed, so that the tumor recurs after a certain time. Moreover it must be borne in mind that unless every gland is examined in serial sections, minute points of metastasis may be overlooked. Such minute metastases have from time to time been noted, even though, for reasons of economy, it has been impractical to make more than a few sections from each gland. The gross appearance of the gland gives no reliable information on the question of metastasis.

Five-Year Results

The crucial test of the value of iliac lymphadenectomy lies in the analysis of the five-year salvage. To compare results in one institution with those in another is most unsatisfactory. Methods of classification into groups and methods of therapy, even though labeled the same, are

found that the external iliac vein and even the external iliac artery can be ligated and a section of the vessel removed with the adherent gland (Fig. 6), I have not hesitated to go ahead with this radical procedure. In none of the six patients in whom this was done was the resultant circulatory disturbance more than temporary. In five cases the vein and in one the artery was resected. Three of these cases which were done between two and one-half and over four years ago showed large metastases in the lymph gland removed in conjunction with the vessel, and all three are still free of recurrence. In one patient, two hypogastric glands were removed with a section of the external iliac vein. The hard gland adherent to the vein, showed no carcinoma, only fibrous strands with a rim of lymphocytic tissue, whereas the nonadherent softer gland lying beneath the resected vein showed a large cancer metastasis. I am at a loss to explain the findings in this case.

Hemorrhage was not infrequently an operative complication, especially since wider dissections have been practiced. In eleven patients the hemorrhage was disturbing but in no case was it fatal. Almost always the bleeding originated in the plexus of veins at the point where the internal iliac vein divides into its branches. These veins are very friable. In the first cases, I tried to catch these veins with forceps and attempted to pass a needle with ligature around them. Invariably the needle would puncture another vein and the bleeding increased. Three of the earlier cases of severe hemorrhage were left open with clamps and a gauze pack to control the bleeding. Clamps and gauze were removed in forty-eight to seventy-two hours. Recently the cases have been handled far more successfully by a firm gauze pack with a strip of the rectus abdominis muscle applied against the bleeding area to promote coagulation. In fifteen to twenty minutes the bleeding was usually controlled and the operation could be concluded. In two cases a small gauze pack was left in the broad ligament for forty-eight hours. In the remaining 6 cases the bleeding was fully controlled and the pack removed before closure. This excessive bleeding can usually be avoided by more gentle manipulations in the deeper portions of the broad ligament.

Injuries to important viscera or nerves are rare. The bladder is out of the operative field. The ureter must be watched especially if large cancerous glands are present as it may then be adherent to them and stripped off of its normal attachment to the posterior sheath of the peritoneum. Once I ligated the ureter but without harmful result to the patient. Once the obturator nerve was resected with an adherent obturator gland but produced only temporary discomfort.

Associated Conditions

In five patients a supravaginal hysterectomy had been previously done. In these cases of cancer of the cervical stump, the technique of the lymph gland removal was not appreciably complicated. In one patient an operable adenocarcinoma of the corpus was found to be associated with the inoperable squamous-celled carcinoma of the cervix and the corpus was removed in conjunction with the lymphadenectomy. I have also recently done an iliac lymphadenectomy (not included in this series) in a case of primary cancer of the upper vagina. This patient with complete local regression following radiation showed cancer in the obturator glands of both sides and died two years later of a recurrence in the right sacral gland.

ated with lymph gland removal and 118 cases of the same group in which radiation alone was used. During this period I subjected a certain number of the Group II cases on my service to radiation only and during Dr. Gellhorn's service all the Group II cases were subjected to radiation without iliac lymphadenectomy. The staff of associates, hospital material, method of classification, and technique of x-ray and radium treatment were identical. Four cases could not be traced after a period of two or more years. In each case they were considered as dead from the time of last information. The percentage of five-year survival was over 15 per cent better in patients who had the additional procedure of iliac lymphadenectomy; or, to put it from the standpoint of patients saved, over 68 per cent *additional* were saved by this operation.

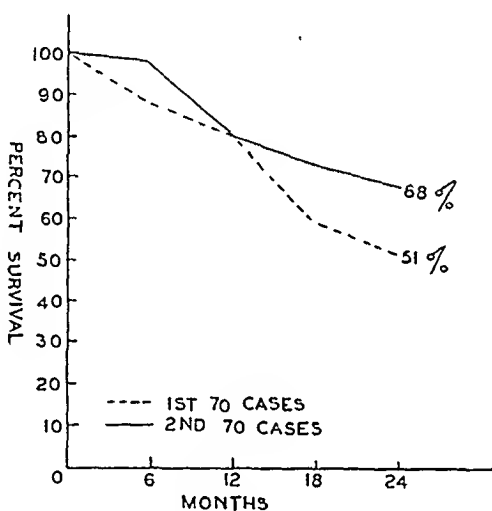


Fig. 9.—Two-year survival curves of the first 70 cases of iliac lymphadenectomy compared with the second 70 cases. Better results in the second series, largely due to improved methods of radiation and more extensive gland removal.

By dividing up the 70 cases treated over five years ago in accordance with whether or not cancer was found in the lymph glands removed, we find an interesting comparison as shown in Fig. 8. As was to be expected, the salvage was definitely less where cancer was found present, the ratio being approximately 2 to 1. On the other hand it is clearly shown that even in the presence of cancer metastasis in the lymph glands, the patient is not necessarily doomed to die. This has been strikingly proved by me in my reports on vulvar cancer. It is also true to a lesser degree of cervix cancer. The case records tabulated in Table I show in brief the history and findings of nine patients having cancer metastasis in the lymph glands that survived longer than four years. Of particular interest are Case 1, now over twelve years free of recurrence, and Cases 7 and 9, in which a metastatic gland adherent to the external iliac vessels required resection of the vessel in order to remove the gland.

likely to be different. It was therefore fortunate that for a five-year period through the alternating six months' services of Dr. Gellhorn and myself at The Barnard Free Skin and Cancer Hospital, a fair basis for comparison was obtainable. As shown in Fig. 7, we have the five-year survival curve of 70 cases of Group II (League of Nations classification) cancer of the cervix in which radiation of the cervix was associ-

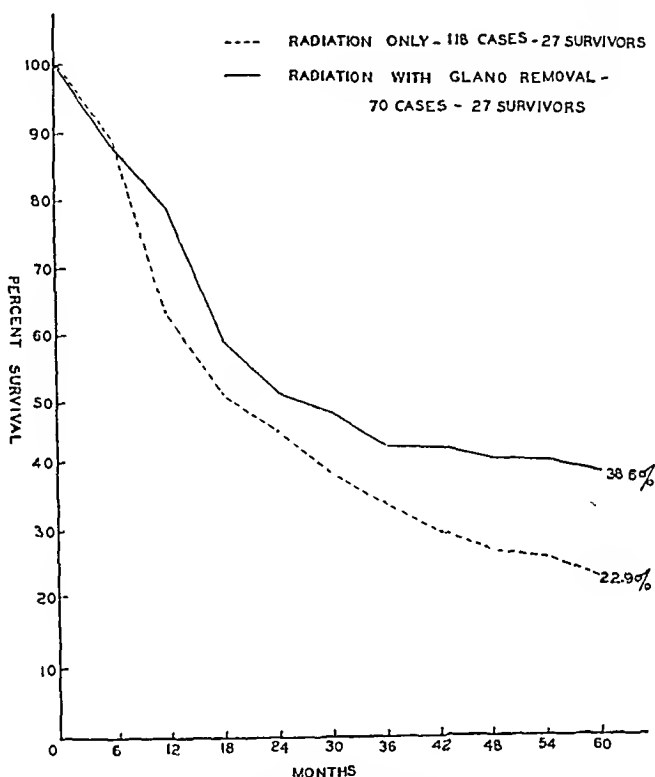


Fig. 7.—Five-year survival curves of two series of cases treated at Barnard Free Skin and Cancer Hospital, by similar radiation, one *with*, and one *without* iliac lymphadenectomy.

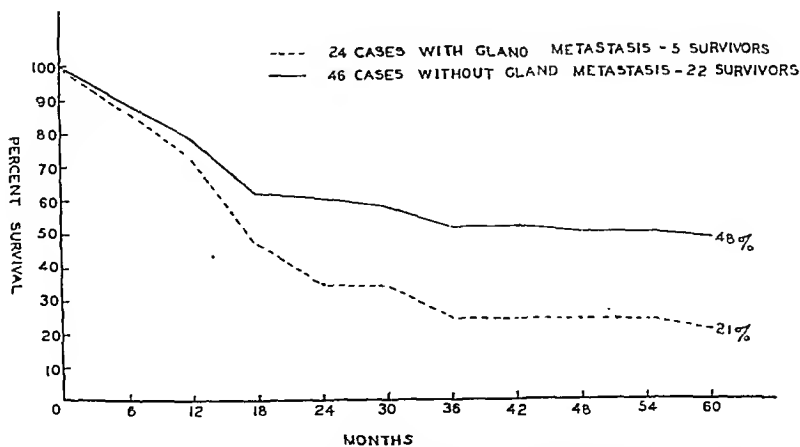


Fig. 8.—Five-year survival curves of 46 iliac lymphadenectomies without cancer present in removed lymph glands, compared with 24 cases with cancer metastasis.

TABLE I. CASES OF CERVIX CANCER WITH LYMPH GLAND METASTASIS SURVIVING LONGER THAN FOUR YEARS

CASE RECORD AGE	SYMPTOMS	INVOLVE- MENT	X-RAY TREATMENT	RADIUM TREATMENT	OPERATIVE NOTES	GLANDS	SUBSEQUENT COURSE
(1) S. S. No. 45286 (51 yr.)	Vaginal bleeding 6 months	Cauliflower lesion. Both para- metria involved	None	Oct. 14, 1930 4,900 mg. hr. Dec. 23, 1930 800 mg. hr. Total 5,700 mg. hr.	Oct. 14, 1930 Two palpable hypogastric glands removed 8 radon seeds introduced abdominally in para- metria	Left hypogastric gland, size of wal- nut, full of cancer	Complete local regres- sion Clinically well, Nov. 6, 1942 (12 yr.)
(2) L. S. No. 45691 (42 yr.)	Bleeding 4 months	Both para- metria in- filtrated	None	Dec. 2, 1930 2,850 mg. hr. Dec. 30, 1930 1,725 mg. hr. 1931-1933 3,600 mg. hr. Total 8,175 mg. hr.	Dec. 2, 1930 Typical operation with radon seed abdominal implantation	Four glands removed Large metastasis in left hypogastric	Repeated small local re- currences Jan. 23, 1935, left in- guinal gland contain- ing cancer removed Died Oct. 5, 1935, re- current (4 yr., 10 mo.)
(3) I. F. No. 48693 (40 yr.)	Bleeding for several months	Parametria and vag- inal fornix in- volved	Feb. 2, 1932 1,800 r. units Sept. 13, 1932 700 r. units	Nov. 10, 1931 3,350 mg. hr. Dec. 22, 1931 1,200 mg. hr. Total 4,550 mg. hr.	Nov. 10, 1931 Typical operation with radon seed abdominal implantation	Four glands removed Two hypogastric glands metastatic	Clinically well but ureterovaginal fistula developed Dec. 8, 1932 Recurrence developed in 1939. Died Aug. 1, 1939 (7 yr., 9 mo.)
(4) A. C. No. 48954 (31 yr.)	Discharge 2 months	Slight para- metrial involve- ment	None	Dec. 15, 1931 3,400 mg. hr. Jan. 26, 1932 1,200 mg. hr. Total 4,600 mg. hr.	Dec. 15, 1931 Typical operation with radon seed abdominal implantation	Seven glands removed Left hypogastric showed cancer	Uneventful course Clinically well June 16, 1942 (10 yr., 6 mo.)

Since there was considerable improvement in the radiation technique employed since 1937, we are anticipating better final results in the group of cases operated since that time. An indication of this is given in Fig. 9 in which we compare the two-year salvage of the first 70 cases with the second 70 cases in my series. The result of better technique is apparent in the second year.

Arguments Against Iliac Lymphadenectomy

1. It may be claimed that this operation is a highly technical procedure, attended by a considerable mortality and complications. The experience in these 175 operations has demonstrated it as a relatively safe and simple procedure, once certain points in anatomy and technique are learned. A short period of training should enable the average surgeon to acquire the necessary skill.

2. A further objection that has been raised is that the operation does not constitute a block dissection as practiced in breast and oral cancer. In a sense it must be acknowledged that this is true. On the other hand, anatomical conditions in the pelvis differ greatly from those in the axilla and neck. In the latter the lymph glands lie in a more or less continuous mass of fat and connective tissue that can be removed en masse. In the pelvis the important tributary lymph glands lie in a more veil-like sheath of loose connective tissue, pocketed between and beneath the large vessels. While it is not feasible on this account to remove them in continuity, we can clean out the lateral half of the broad ligament area on each side as thoroughly as in an axillary dissection. Just as the latter does not ordinarily include the supraclavicular chain, so the iliac lymph gland operation does not include the sacral glands. My procedure is at least 80 per cent complete and hence I believe is amply justified. Extrapelvic gland metastasis, as has long been demonstrated, is not the rule, even in cases coming to autopsy.

3. Finally, the operation has been opposed by radiologists, who claim that with recent improvements in deep roentgen therapy, cancer in the pelvic lymph glands can be destroyed by radiation as completely as removed by surgery. I do not deny the value of such prolonged radiation and the microscopic studies made in removed lymph glands in my cases show that after heavy radiation, cancer is less frequently noted. Nevertheless we have no evidence that this apparent disappearance of metastases is permanent. It does not compare in therapeutic certainty with the surgical excision of these glands. It has long been demonstrated that the removal of axillary lymph glands in breast cancer even when found free of metastases is justified by clinical experience. In similar manner I feel that even though cancer may be found in the pelvic lymph nodes in not more than one out of every four or five cases after heavy x-radiation, the surgical excision of such nodes is justified.

Summary

1. One hundred and seventy-five cases of Group II cervix cancer were subjected to iliac gland removal with radiation of the primary tumor. The operative mortality in this group was 1.7 per cent with a mortality of 0.7 per cent in the last 140 cases.

2. The five-year survival rate of 70 cases operated previous to October, 1937, was 38.6 per cent. Comparing this with a five-year survival of 22.9 per cent in 118 similar cases treated by radiation alone, there was a 68 per cent greater salvage when the lymph gland removal was added to the radiation treatment.

3. Cancer was found present in the lymph glands in 26.8 per cent of the 175 cases operated upon. Even in those cases with demonstrated metastases, a five-year salvage of 21 per cent was obtained.

4. This experience extending over a period of twelve years has, I believe, firmly established iliac lymphadenectomy as a valuable adjunct in the treatment of Group II cancer of the cervix.

AN ANALYSIS OF SOME FACTORS ASSOCIATED WITH THE DEVELOPMENT OF PRE-ECLAMPSIA

With Special Reference to Extracellular Water Measurements in 1,388 Patients

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MANY publications indicate that rapid or excessive weight gain often points to water retention which may be a harbinger of pre-eclampsia. It has been recognized that many patients having abnormal weight gains have not accumulated excessive water, but rather have laid down protoplasm or fat (Waters¹).

In a previous paper,² we have reported measurements of the thio-cyanate-available water (roughly equivalent to the extracellular water) in 180 cases of human pregnancy. Patients who had excessive available water, but who were clinically normal, showed a 23.1 per cent incidence of pre-eclampsia developing subsequent to the test. In contrast, patients with normal water had a toxemia incidence of only 1.42 per cent.

Since we were interested in selecting potential toxemia patients for special study, we have routinely determined the available water in almost all of our clinic patients (who were registered early enough) from October, 1941, through June, 1942. In all, and including the published series, 1,388 patients were given the test at least once; 552 of these had

(5) H. S. No. 66682 (59 yr.)	Bloody discharge at intervals for 2 years	Right parametria thickened	Nov. 19, 1936 3,200 r. units Feb. 13, 1941 to April 8, 1941 8,000 r. units	Jan. 2, 1937 4,000 mg. hr. Oct. 18, 1941 1,400 mg. hr. Total 5,400 mg. hr.	April 24, 1937 Difficult operation, ligated external iliac vein	Nine glands removed Cancer metastasis in left and right hypogastric	Small local recurrence Oct. 1, 1941 Clinically well July 3, 1942 (5 yr., 3 mo.)
(6) G. S. No. 69060 (54 yr.)	Bleeding every 2 weeks for 1 year	Both parametria thickened	July 23, 1937 5,600 r. units	Aug. 11, 1937 5,000 mg. hr. Jan. 26, 1938 680 mg. hr. Total 5,680 mg. hr.	Oct. 8, 1937 Operation difficult Gland adherent to right external iliac vein.	Six glands removed Large metastasis in right hypogastric gland	Clinically well Aug. 30, 1942 (5 yr.)
(7) A. W. No. 70305 (51 yr.)	Bleeding for 4 months	Left parametria thickened Myomatous uterus	Nov. 9, 1937 5,600 r. units	Dec. 29, 1937 2,500 mg. hr. Jan. 5, 1938 2,500 mg. hr. Total 5,000 mg. hr.	Dec. 11, 1937 Operation including supracervical hysterectomy for myomata Resection of left external iliac artery with adherent lymph gland	Five glands removed Large necrotic metastasis in left hypogastric	No sequelae from ligation of artery Clinically well July 6, 1942 (4 yr., 7 mo.)
(8) G. B. No. 70678 (39 yr.)	Prolonged menses 2 years	Both parametria involved	Dec. 17, 1937 5,600 r. units	Jan. 29, 1938 3,500 mg. hr.	Jan. 5, 1938 Typical operation	Ten glands removed Left obturator showed cancer	Clinically well Oct. 28, 1942 (4 yr., 10 mo.)
(9) E. W. No. 71896 (46 yr.)	Bloody discharge 1 year	Left parametria thickened	May 5, 1938 5,000 r. units	Feb., 1938 7,500 mg. hr. (?) given elsewhere	April 23, 1938 Difficult operation Left external iliac vein resected with adherent gland	Nine glands removed Large metastasis in left hypogastric gland	Clinically well June 30, 1942 (4 yr., 2 mo.) (See Fig. 6.)

Of the 107 cases of pre-eclampsia, 44, or 41.1 per cent, were in the group of patients showing normal water. Thus the test often failed to select patients who subsequently developed pre-eclampsia. An analysis of such failures reveals several causes which operated separately or together.

Causes for Failure of Test.—1. When the measurement of available water was begun as a routine procedure on our clinic patients, the determination was made at the thirty-fourth week of pregnancy. It was

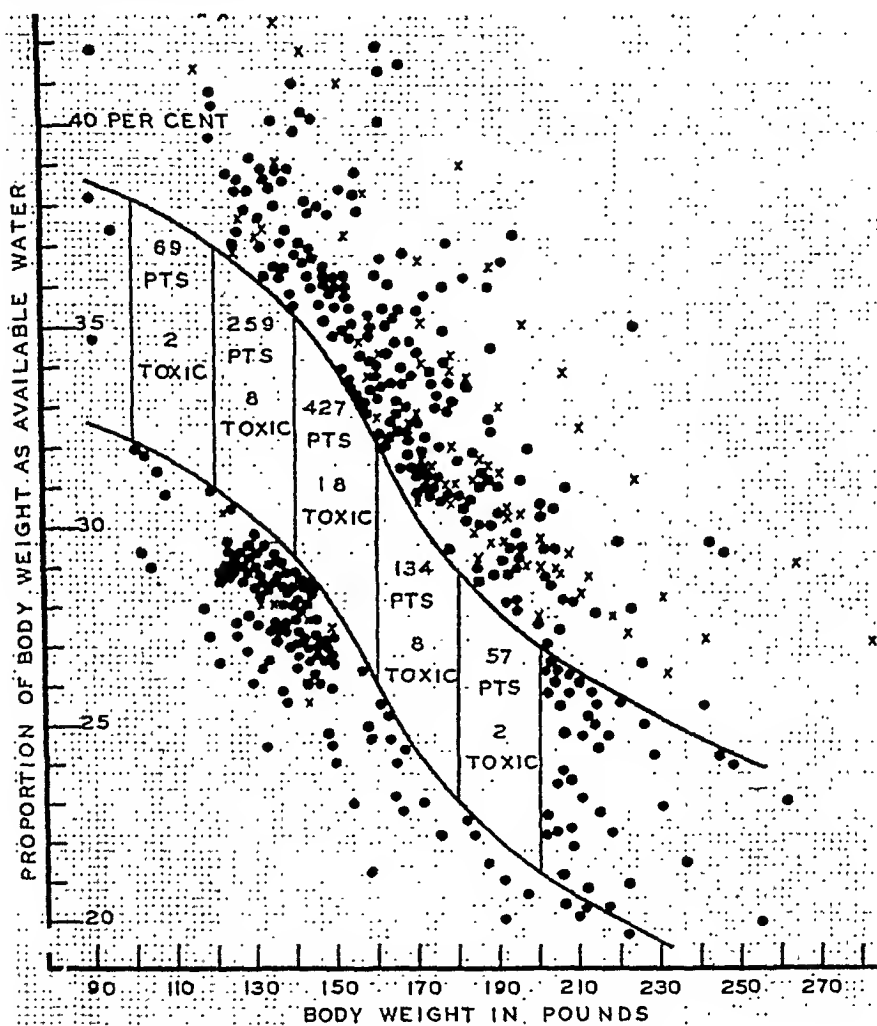


Fig. 1.—The distribution of normal and abnormal values for extracellular water in 1,388 pregnancies. The curves were drawn by the same criteria as previously described.²

• = Normal pregnancy
x = Toxemia

soon found that this was frequently too early, since many patients began to accumulate abnormal amounts of available water after this time. As a result of this finding, the routine was changed so that the first measurement of available water was made at the thirtieth to thirty-third week, with the test being repeated at the thirty-fifth to thirty-seventh week. Many (42) patients had normal proportions of water in the first test, and excessive water when repeated; a number of these subsequently

2 or more tests. All measurements were made after the thirtieth week of gestation, usually at about thirty-two to thirty-six weeks.

In the present study, we shall analyze this series for a number of factors which might conceivably affect the incidence of excessive water and of toxemia. An evaluation of the test will be attempted.

In the following discussion, the terms "available water," "extracellular water" and "water" will be used more or less interchangeably. This, of course, is inexact but will save circumlocution.

Methods

Each patient was given 1,000 mg. of sodium thiocyanate in fruit juice, by mouth. (In the first 180 cases, previously reported, the thiocyanate was given intravenously.) The patient was asked to save all of her urine and come back the following morning, at which time the urine collection was completed, and a blood sample was drawn with minimal or no stasis. The period thus allowed for the distribution of thiocyanate in the extracellular water varied from eighteen to twenty-four hours, and was usually close to twenty-one hours.

Thiocyanate in serum and urine was determined in duplicate with the Evelyn photoelectric colorimeter, by a method described elsewhere.³ The completeness of urine collection was checked by measurement of the creatinine excretion, using the method of Folin.⁴ The test was discarded if considerable volumes of urine obviously had been lost.

The "available water" was calculated in terms of percentage of body weight, since we felt that the usual formula for surface area might not be valid in late pregnancy.

Serum proteins were determined in duplicate, one sample by the method of Wong⁴ and one by that of Howe and Koch and McMeekin.⁵ Recorded results checked within 2 per cent.

Relation of Excessive Water to Toxemia

In the tables to follow, the number of patients will not always agree because the specific information for many patients was not available, or the patients had not been observed over long enough a time in pregnancy. Two-thirds of all patients with excessive extracellular water were placed on low salt diets as soon as the abnormality was found. This may have affected the incidence of toxemia.

Fig. 1 shows the distribution of normal and abnormal values for the available water. The incidence of excessive water in the 1,388 patients was 19.96 per cent, in good agreement with the 21.66 per cent found in the first series of 180 patients.

The incidence of pre-eclampsia in the whole series was 7.71 per cent. In patients with excessive water, the incidence of subsequently developing pre-eclampsia was 22.75 per cent (compare 23.1 per cent in the original series), while in patients with normal water at the time of the test, the toxemia incidence was 3.96 per cent. This last figure is somewhat higher than the 1.42 per cent originally found, but will be explained below. From these data, it appears that the patient with excessive water was, on the average, about 6 times as likely to develop pre-eclampsia as was the patient with normal water. More frequent measurements of the available water would magnify this difference.

TABLE I. THE RELATION OF SERUM PROTEINS TO WATER RETENTION AND TOXEMIA

DEGREE OF ABNORMALITY IN AVAILABLE WATER	NORMAL WATER		DEGREE OF AVAILABLE WATER INCREASE								TOTALS
	LESS THAN 5.75	MORE THAN 5.76	<5.75	>5.76	<5.75	>5.76	<5.75	>5.76	<5.75	>5.76	
Cases	25	61	19	75	6	15	6	13	6	13	266
Average serum protein grams per 100 ml.	8.00	9.84	21.05	16.00	18.75	23.33	33.33	6.67	66.7	38.5	6.12
Percentage of cases with protein <5.50											11.65
Percentage of cases with protein <5.75											27.05
Incidence of toxemia, per cent											17.30
Serum protein level, grams per 100 ml.											
Cases	25	61	19	75	6	15	6	13	6	13	266
Incidence of toxemia, per cent	8.00	9.84	21.05	16.00	18.75	23.33	33.33	6.67	66.7	38.5	17.30

developed pre-eclampsia. Thus water retention often did antedate hypertension, but this observation could be missed by measuring the available water too early. It is this factor which accounts for the higher incidence of toxemia in the "normal water" group in the present paper, as compared with the original series in which nearly all tests were done in the last three to four weeks of pregnancy.

2. We shall demonstrate in a separate study that the restriction of salt in the diet will markedly reduce the volume of available water. Such reduction in available water to normal levels does not uniformly prevent the appearance of hypertension and the rest of the pre-eclamptic syndrome. This fact may often account for the finding of normal extracellular water not only in the "pretoxic" patient, but also in certain patients with manifest toxemia.

Of the 44 patients developing toxemia after a test had shown normal water, 6 had been on a diet, the nature of which was not specified in the chart. Of the 38 remaining, 25, or 65.8 per cent, had been placed on a 2 Gm. salt diet prior to the test. It seems quite possible that the available water in these cases may have been reduced, and that the test was done too late to show any abnormality which may have existed.

3. Cases of eclampsia, and of noneconvulsive toxemia, without clinical edema are not uncommon. Whether such cases occur without any abnormal water retention is unknown, since the body may gain water up to 10 per cent of its weight without visible edema. While a few of our patients with toxemia have had normal values for available water (i.e., not even occult edema was present), dehydration treatment had been used prior to the test. If toxemia does occur without even occult edema, and on the average dietary salt intake, then measurement of available water could not be of prognostic value in such cases.

4. Some patients classified as having pre-eclampsia may rather have labile blood pressures. Possibly these are latent hypertensives who have a simple increase in blood pressure as they approach term. Measurement of occult edema would not be of value in predicting such "toxemias."

5. The possibility of intracellular water retention must not be ignored. Intracellular water is inaccessible to measurement by the thio-cyanate method.

Factors Possibly Affecting the Incidence of Increased Extracellular Water and of Toxemia

1. *Serum Proteins.*—It is well known that the plasma proteins play a leading role in maintaining the fluid balance between the blood and the extracellular space of the body. The filtration of fluid out through the capillary walls is impelled by the intravascular hydrostatic pressure. This filtration, normally, is nicely balanced by capillary reabsorption attributable to the oncotic pressure of the proteins. Depletion of the proteins results in decreased reabsorption of the filtrate and edema may occur, as in nephrosis or nutritional edema. Goudsmit and Louis,⁶ in a quantitative study, found that a decrease of 1 Gm. of protein per 100 ml. of serum resulted in an increase in extracellular water amounting to 3.8 ± 0.8 per cent of the body weight. Strauss⁷ has attributed toxemia of pregnancy (as distinguished from vascular disease) to water retention caused by lowered plasma proteins or excessive sodium intake, or both.

5. *Weight*.—Matthews and Der Brucke¹⁰ have demonstrated that toxemia of pregnancy shows an increased frequency in women weighing more than 200 pounds. We have divided our patients into weight groups, and found that as the weight increased there is a progressive rise in incidence both of abnormally high water and of toxemia. The increasing incidence of toxemia occurs in those patients with abnormal water, not in those with normal water (Table II).

6. *Weight Gain*.—Since weight gain has been considered important in that rapid or excessive gain may be a premonitory sign of toxemia, we have analyzed our data in several ways, looking for a correlation between amount or rate of weight gain and the incidence of excessive water and toxemia.

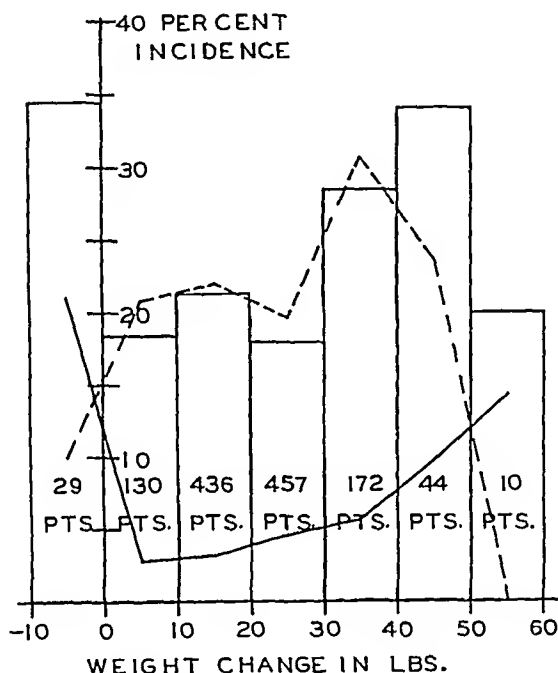


Fig. 2.—The relation between total weight change in pregnancy, and the incidences of excessive available water and toxemia. The columns \square give the incidence of excessive water, and the numbers in each column refer to the number of patients in group. The solid line gives the incidence of toxemia in patients with normal available water at the time of the test. The broken line gives the incidence of toxemia in patients with excessive available water.

A. The total weight gain to the time of the last measurement of available water showed no correlation with the amount of water until the gain exceeded 30 pounds. Even then, the incidence of excess water was no greater than in patients who had lost rather than gained weight. However, nearly all patients losing weight did so in consequence of an obesity diet. As demonstrated above, obese patients have a greater incidence of abnormal water.

The incidence of toxemia increased slightly as the weight gain rose (Fig. 2).

B. Rapid gain in weight at any time in pregnancy, prior to the last test, seemed to bear no relation to the incidence of excessive available water. In 709 patients gaining less than 6 pounds per month, the incidence of excessive water was 23.58 per cent; in 483 patients gaining more than 6 pounds, it was 18.02 per cent. The incidences of toxemia were 8.32 and 7.66 per cent, respectively.

We have determined the serum proteins in 86 patients with normal available water, and in 180 with excessive water. The results (Table I) indicate no significant difference between the normals and patients with varying degrees of water retention, either in average levels, or in the distribution of low values. The average serum protein checks well with many published data for normal pregnant women.

A correlation between the serum proteins and the incidence of toxemia does seem to exist, if the available water is markedly abnormal. As Table I indicates, toxemia is more frequent in patients with 3- and 4-plus abnormally high water who also have serum proteins of less than 5.75 Gm. per 100 ml.

2. *Hemoglobin*.—Peters and Eisenman⁸ have demonstrated that low hemoglobin levels may often be associated with edema, even in the presence of high normal serum proteins. We found that the average hemoglobin was the same in patients with or without excessive water, and with or without toxemia of pregnancy. However in the patients with excessive water, 26.7 per cent had hemoglobins of less than 80 per cent while in the normal group, 15.7 per cent had hemoglobins below 80 per cent. (Hemoglobin was determined by the Sahli method, and 14.5 Gm. per 100 ml. was considered as 100 per cent.)

3. *Rh Factor*.—The Rh factor, which seems to be a causative agent in erythroblastosis foetalis, has been suggested as perhaps related to toxemia of pregnancy. A possible relation to edema is seen in the fetal hydrops often found in erythroblastosis. The Rh factor was determined in 238 of our cases, and no correlation with excessive water is evident. In 203 Rh positive cases, the incidence of excessive water was 22.16 per cent; in 35 Rh negative cases, 6, or 17.14 per cent, showed increased water. The incidence of toxemia in the Rh positive group was 9.86 per cent and in the Rh negative was 8.57 per cent, not a significant difference. The incidence of Rh negative women was 14.7 per cent, in good agreement with the 14.0 per cent reported by Levine, Vogel, Katzin and Burnham⁹ in 1,035 cases.

4. *Parity and History of Toxemia*.—The incidence of excessive water was greater in the multiparas (25.3 per cent) than in primiparas (16.3 per cent). Further analysis shows that this difference is accounted for by those women having a history of previous toxemia, of whom 51.5 per cent had an increased amount of water and 21 to 32 per cent a recurrent toxemia.

Perhaps the disturbance resulting in toxemia in an earlier pregnancy is still operative in some degree in about half the cases, as shown by the water retention.

TABLE II. THE RELATION BETWEEN BODY WEIGHT AND THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

BODY WEIGHT		LESS THAN 120 POUNDS		121-160 POUNDS		161-200 POUNDS		MORE THAN 201 POUNDS	
Cases		86		889		343		70	
		CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Incidence of excessive water		7	8.14	100	11.25	137	39.95	33	47.15
Incidence of toxemia	All cases	4	4.65	48	5.41	44	12.83	11	15.73
	Cases with normal water	2	2.53	32	4.06	10	4.86	0	0.00
	Cases with excessive water	2	28.58	16	16.00	34	24.81	11	33.33

The incidence of excessive water is not influenced by the variability of the blood pressure. The incidence of toxemia shows no significant change so long as the maximal variability in systolic blood pressure is less than 20 mm. Hg; with greater lability of blood pressure, the toxemia incidence nearly doubles, both with normal and with excessive water (Table IV). Thus "warning rises" in systolic pressure, if greater than 20 mm. Hg do have some significance.

TABLE IV. THE RELATION BETWEEN THE MAXIMAL VARIATION IN SYSTOLIC BLOOD PRESSURE AND THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

SYSTOLIC VARIATION MM. HG		LESS THAN 10	11-15	16-20	21-25	MORE THAN 26
Cases		339	239	278	179	193
Incidence of excessive water, per cent		21.83	21.36	18.72	25.12	23.82
Incidence of toxemia	All cases, per cent	4.13	7.11	6.48	11.18	16.59
	Cases with normal wa- ter, per cent	1.13	4.79	3.54	4.48	8.85
	Cases with excessive water, per cent	14.88	15.68	19.23	31.10	30.44

8. *Usual Level of Blood Pressure.*—The incidence both of excessive water and of toxemia increases with rise in the usual level of blood pressure. In the present series, no patient developed toxemia if the blood pressure had been consistently less than 105/60 mm. Hg preceding the measurement of available water. (Analysis of large groups of toxemias will, of course, show considerable numbers of patients with low blood pressures prior to the onset of toxemia.) Of all patients with normal pregnancies, 73.4 per cent never showed a blood pressure as high as 130 mm. Hg in the systolic, or 80 mm. Hg in the diastolic. In contrast, 72.5 per cent of those developing pre-eclampsia subsequent to the measurement of available water *did* show pressures exceeding 130/80 on at least one occasion, and their blood pressures were usually above 120/70. From the data in Table V and especially from Fig. 3, it appears that the incidence of toxemia increases with 2 factors, either of which is effective alone, and that when these factors are both present, a very high incidence of toxemia may be expected. The factors are increasingly high level of usual blood pressure and the presence of excessive water. Of these 2, the blood pressure level may be more fundamentally important since, excluding chronic hypertension, the incidence of excessive water (accumulated late in pregnancy) seems to increase with each increment in

TABLE V. THE RELATION OF THE USUAL LEVEL OF SYSTOLIC BLOOD PRESSURE TO THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

USUAL SYSTOLIC PRESSURE, MM. HG		90-99	100-109	110-119	120-129	MORE THAN 130
Cases		50	267	454	376	125
Incidence of excessive water, per cent		4.00	16.86	19.62	26.06	28.80
Incidence of toxemia	In all cases, per cent	0.00	2.25	4.41	14.10	17.60
	Cases with normal wa- ter, per cent	0.00	0.90	2.46	8.28	9.00
	Cases with excessive water, per cent	0.00	8.89	12.37	30.62	38.90

C. The weight gain per week, within a month before the test, did not bear any relation to the incidence of excessive available water until the weight gain exceeded 4 pounds per week. Such large gains, which occurred in only 2.6 per cent of all patients, doubled the incidence of excessive water. The incidence of toxemia did increase somewhat as the rate of weight gain became greater. The effect was not well marked until the gain reached 4 pounds per week, and appeared only in those patients with *normal* available water. If these rapid gains represent water retention, the water may be held intracellularly.

D. The weight gain per week after the test tended to be greater in those patients who had increased available water. The abnormal tendency shown by the water retention seemed to predispose to further gain. Ignoring patients who lost weight, in the normal water group, 829 patients gained an average of 1.71 pounds per week after the test, while 198 patients with excessive water averaged 2.21 pounds per week.

The incidence of toxemia increased with the rate of weight gain following the test. This correlation was found only in patients whose available water had been normal when measured (Table III). These patients who gained weight rapidly and went on to develop pre-eclampsia presumably gained water excessively after the test.

TABLE III. THE RELATION BETWEEN RATE OF WEIGHT GAIN AFTER THE TEST AND THE INCIDENCE OF TOXEMIA

WEIGHT CHANGE PER WEEK, AFTER TEST		LOSS IN WEIGHT	GAIN IN WEIGHT, POUNDS PER WEEK								
			0-1	1-1½	1½-2	2-2½	2½-3	3-3½	3½-4	4-4½	MORE THAN 4½
Cases		137	256	174	179	139	124	44	45	27	39
Incidence of toxemia	In all cases; per cent	12.41	6.62	6.90	5.59	7.20	7.27	13.63	13.34	7.41	12.82
	Cases with normal water	8.14	3.30	2.76	1.97	1.93	5.88	8.83	9.09	5.56	8.00
	Cases with excessive water	19.60	23.00	27.60	25.95	22.86	13.64	30.00	25.00	12.50	25.00

7. *Variability in Blood Pressure.*—Browne¹¹ has described a "warning rise" in blood pressure occurring during pregnancy, which may be observed on a single occasion. He believes that patients showing such upward spikes in pressure are likely to develop toxemia as they approach term. Accordingly, we have analyzed our data in several ways, seeking a relationship between variability of blood pressure and the incidence of excessive water and of toxemia. The rise in blood pressure was broken down into groups of 5 mm. increments, and was calculated as (a) the difference between the highest and lowest pressures, (b) the difference between the highest and the usual (or average, if variable) pressure, and (c) the difference between the pressure at the time of the test and the usual (or average) pressure. All analyses were based on blood pressures observed before the last measurement of available water, and include both systolic and diastolic readings. Since the results of all analyses are about the same, only one set of data will be presented, those of the maximal variation in systolic pressure. In general it may be said that the usual level of blood pressure (see below) is more important than the variability in predisposing to toxemia.

Miscellaneous Observations

1. *Time From Test to the Appearance of Hypertension.*—The average period from the demonstration of excessive water to the appearance of hypertension was about four weeks. In those patients having excessive water and subsequently developing pre-eclampsia, 60 per cent showed the first abnormal blood pressure readings in two and one-half to five and one-half weeks after the test. In a few cases (4 per cent) as long as ten weeks elapsed between the finding of excessive water and the appearance of hypertension. In some other cases hypertension may have appeared before the water retention, although this is not certain as pointed out above. A few patients, under dehydration treatment, did have pre-eclampsia without excessive water being found either before or after the blood pressure rose.

In patients developing pre-eclampsia after the test had shown a normal available water level, the average period between the test and the first elevation in blood pressure was nearly six weeks. Thus there was time for many of these patients to accumulate water before developing hypertension. Repeated tests often demonstrated that this had happened (see above).

2. *Relation of Weight Gain to Water Gain.*—In 552 cases, 2 or more measurements of available water were made in the last ten weeks of pregnancy. Comparison of the change in available water with the change in body weight reveals that in 42 per cent of all cases the gain in water exceeds the gain in weight, and in 8.6 per cent there is a gain in water with a loss in body weight.

The simplest of several possible explanations would be that late in pregnancy intracellular water shifts into the extracellular compartment. Dieckmann¹³ has suggested such a shift in water to account for the sudden appearance of edema in certain toxemia patients, and McPhail¹⁴ believes that one of the central features of toxemia is cell dehydration arising out of an extensive shift of intracellular water into the interstitial spaces. In many respects toxemia of pregnancy is characterized by exaggerated changes, which in lesser degree are normally incident to pregnancy. Perhaps movement of water out of the cells is a normal occurrence in late pregnancy, and in the toxic disturbances the shift is unusually great.

This hypothetical shift in water (if such it be) is more marked in patients who have an abnormally high available water level, and is still more marked in patients who are normal in the first test and abnormal in the second.

Conversely, in patients who lose weight and water under salt restriction, the loss in available water is almost always greater than the weight loss. This suggests that some extracellular water may shift back into the cells, probably because extracellular sodium is depleted. These data will be presented in more detail in another paper.

The incidence of excessive water increases when the disproportion between water gain and weight gain increases. The incidence of toxemia does not show so regular a correlation.

The average increment in available water, toward the end of pregnancy, is about 250 to 300 ml. per week in patients whose dietary salt intake is unrestricted. Apparently this gain tends to be maintained regardless of changes in body weight. A high proportion of patients who add less than one-half pound per week in body weight will gain

blood pressure. We cannot say whether the higher arterial pressure carries through the arterioles to the capillaries, and thus increases filtration, which in turn leads to an accumulation of edema water. This is probably not the case in most forms of hypertension, since the peripheral resistance is thought to be localized in the arterioles. In consonance with this belief, we found excessive water in only 3 of the 18 patients who were known cases of chronic hypertension. However, in pre-eclampsia the venous pressure has been reported as lying at the uppermost limits of normal,¹² which suggests that the capillary pressure may be slightly increased.

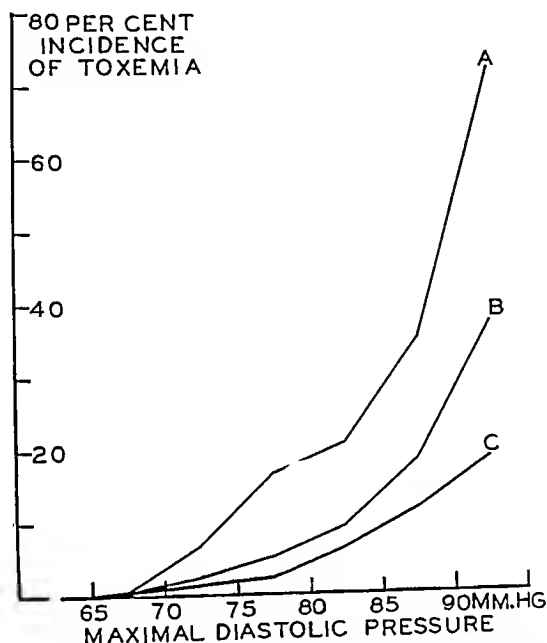


Fig. 3.—The relation between the maximal diastolic pressure as observed at any time during pregnancy, and the incidence of preeclampsia. A, patients with excessive available water. B, all patients. C, patients with normal available water at the time of the test.

9. *Maximal Blood Pressure.*—The maximal blood pressure observed prior to the measurement of available water was found to have a marked effect upon the incidence of toxemia, and a somewhat lesser effect upon the incidence of excessive water. Fig. 3 shows that the incidence of toxemia increases very rapidly as higher maximal diastolic readings are observed. All cases used for their graph were considered as not having toxemia at the time of the test. Those whose maximal diastolic pressure reached 90 or more had shown single upward spikes in the blood pressure, often early in pregnancy.

10. *Time Elapsed From Test to Delivery.*—As might be expected, the longer before delivery one measures the available water the lower is the incidence of abnormal findings, and the higher is the incidence of toxemia in patients whose available water was normal at the time of the test. This merely means that the water retention (at least extracellularly) most frequently begins after the thirty-fourth week of gestation.

11. *Degree of Abnormality of Test.*—The toxemia incidence increases as the measurement of available water shows a greater abnormality. This may be seen by reference to Table I.

ever, when excessive available water and lowered serum proteins were found together, there seemed to be an increased predisposition to pre-eclampsia.

5. No definite correlation was found between hemoglobin levels and the incidence of excessive available water.

6. The Rh factor seemed to bear no relation either to the incidence of excessive available water or to toxemia.

7. Women with a history of toxemia in a previous pregnancy had a greatly increased incidence of excessive available water, even though they may not have developed a recurrence of hypertension.

8. The incidence of excessive available water rose with increase in body weight. Heavier women with excessive water showed an increasing incidence of toxemia which was not found when the water was normal.

9. Total weight gain until the time of the test did not have any effect upon the incidence of excessive available water or of toxemia unless the weight gain exceeded 30 pounds.

10. The rapidity of weight gain bore no relation to the incidence either of excessive available water or of toxemia until the gain exceeded 4 pounds per week.

11. The rate of weight gain subsequent to the test was somewhat increased in patients who had abnormally increased available water. From this, and from 9 and 10 it would appear that measurement of available water is a better indicator of developing toxemia than is weight-taking.

12. Spontaneous variability in blood pressure did not affect the incidence of excessive available water. If the variation exceeded 20 to 25 mm. Hg in the systolic, the incidence of toxemia was somewhat increased in patients both with normal and with excessive available water.

13. As the usual level of blood pressure increased, there was a rise in both the incidence of excessive available water and the incidence of toxemia. This did not apply in cases of chronic hypertension, where the incidence of excessive available water was about 17 per cent.

14. In women who developed pre-eclampsia, the average interval of time from the measurement of available water to the appearance of hypertension was four weeks if the water was abnormal and six weeks if the water was normal. In a few cases, water retention preceded hypertension by as much as ten weeks.

15. The rate of gain in available water averaged about 250 to 300 ml. per week toward the end of pregnancy, if dietary salt was not restricted. This gain in water tended to be maintained regardless of weight change.

16. From the disparity between available water gain and weight gain in the normal patient, and between available water loss and weight loss on low dietary salt intakes, it was suggested that intracellular water may normally shift out into the interstitial spaces as pregnancy approaches term.

more available water than can be accounted for by the weight change. Among patients adding weight more rapidly, a small proportion show such marked disparity between water and weight gains.

Evaluation of Test

Unfortunately there is no known way to select in advance patients whose pregnancies will be complicated by toxemia. The determination of extracellular water, at the proper time in late pregnancy, is only a very short step in that direction. In the present series the test has enabled us to pick out 59 per cent of the "pre-toxic" patients but, as pointed out above, more frequent measurement of the available water would improve this percentage. This selection of "pre-toxic" patients does not seem very specific inasmuch as 4 out of 5 of them do not develop the classical syndrome of pre-eclampsia. (In this series two-thirds of the patients had been put on low salt diets as soon as the excessive water was found: this, it is to be hoped, may have occasionally prevented the appearance of hypertension, proteinuria, edema, etc.)

It would appear from Table V that the test is of very little utility in about one-fourth of all patients, i.e., those whose blood pressures have consistently been less than 110/70. In this group of patients, the incidence of excessive water is low, and very few develop toxemia. In the patients with higher levels of usual blood pressure, the measurement of extracellular water does make a partial separation of the "pre-toxic" patients, although a normal test is no guarantee against toxemia. As a single criterion for selecting "pre-toxic" patients, the trend of the blood pressure would seem nearly as reliable as the measurement of the available water, but if both factors are considered together, a much more reliable prognosis may be made.

Apart from the time involved, the cost of a single measurement of available water is about 2.2 cents. One worker can do 20 to 25 patients a day, including everything from explaining the test to patients and administering the thiocyanate through the collection of blood and urine, to the chemical analyses and arithmetic.

Summary and Conclusions

1. Measurements of thiocyanate-available water (roughly equivalent to extracellular water) were made in 1,388 women in the last ten weeks of pregnancy. Two or more determinations were made in 552 of these patients.

2. The incidence of abnormally increased available water was 19.96 per cent.

3. The incidence of pre-eclampsia was 6 times as great in women with excessive available water as in those with normal water. This difference could have been augmented by more frequent measurements of water.

4. No correlation could be found between serum proteins and the incidence and degree of abnormality of excessive available water. How-

CYCLIC VARIATIONS IN THE CERVIX OF THE GUINEA PIG

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CLOSELY coordinated cyclic changes in various structures of the female genital tract have been clearly demonstrated in the past. This has been shown to be true in animals and in the human being. In the past decade, much has been added to our knowledge regarding changes brought about by hormonal influence on genital structures. Contributions dealing with the physiology of the cervix, however, are few in number. In this report are presented our findings regarding the cyclic changes in the guinea pig cervix, which possibly bear a relation to the human subject.

In a discussion of the estrus cycle in the mouse, Allen¹ makes very little reference to the changes in the cervix. Hammond,² in 1927, and Cole,³ in 1930, described a definite series of changes in the cervix of the cow. Grant,⁴ and Cole and Miller⁵ have described structural changes in the cervix of the ewe. In 1932 Westman,⁶ studying the cervix of the monkey, observed relatively narrow cervical glands in the early part of the cycle, and after ovulation noted dilatation of the glands accompanied by a pronounced secretion from the tall epithelium.

Stieve,⁷ in 1927, believed that the cervical epithelium was never in a dormant state. He observed that the cervical glands became larger before menstruation and regressed following the flow. In a study embracing a group of normal patients, presented in a series of papers, Wollner⁸⁻¹⁰ found evidence of a definite cycle in the human cervix. The most characteristic changes occurred in the epithelial elements, namely their destruction at the onset of menstruation, followed by rapid regeneration, proliferation and finally secretory activity after the interval period. He was able to correlate this with the cyclic changes of the endometrium.

The first detailed study of cyclic changes in the guinea pig was made by Hartmann and Olbers¹¹ in 1931. In a series of 36 animals, they found pronounced variations during the estrus cycle. According to these authors, during the diestrus period, the cervical folds are covered with a single layer of columnar epithelium, the folds themselves consisting of a thick nonedematous stroma. The nuclei of the epithelial cells are basally situated and are quite close together. At the beginning of proestrus the layers increase in number, the nuclei shift to the center of the cells, the folds increase in number, and the vessels become congested. In estrus the nuclei disappear, the epithelium separates and is cast off. The stroma during estrus is less dense, the deeper epithelial layers undergoing autolysis with the formation of vacuoles. The whole layer eventually desquamates, following which the fold production begins to decrease. At the beginning of diestrus a simple cuboidal epithelium

17. An evaluation of the measurement of available water was made.

a. In the present series, 59 per cent of "pre-toxic" patients were picked out by the test. This percentage could have been improved by more frequent measurements of the available water.

b. The test was not specific, inasmuch as 80 per cent of the patients showing excessive available water did not develop pre-eclampsia.

c. Patients with blood pressures consistently below 110/70 showed a low incidence of excessive available water, and seldom developed toxemia. This fact indicated that the test was of little use in about one-fourth of all patients.

We wish to acknowledge our gratitude to Drs. S. A. Cosgrove, E. G. Waters, and J. F. Norton for reading and criticizing the typescript. Miss Frances Orsato and Mr. Peter Marotta did most of the creatinine and serum protein determinations. Miss Sara Fellman did the Rh determinations under the direction of Dr. W. H. Somers.

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Spoto, Pompeo: *Labhardt's Subtotal Colpoperineocleisis*, *Ginecologia* 6: 243, 1940.

The author describes, with semischematic drawings, the operative treatment developed by Labhardt and used in the surgical correction of vaginal and vaginouterine prolapse cases. A descriptive connotation for the surgical procedure is "subtotal colpoperineocleisis." The operation is best suited for those elderly patients who have lost their sexual functions.

The surgical procedure is easily carried out under local anesthesia and would appear, according to the author, superior to other and similar operative methods. The primary operative mortality in 171 cases, reported by Labhardt in 1934, was 1.7 per cent, while in 308 cases, up to July, 1939, the mortality rate was 3.9 per cent. The principal cause of death was pulmonary embolism.

A cure of the prolapse condition was effected in 93.5 per cent of the 308 cases. Sixteen patients had a recurrence of their prolapse, and of these, 8 were reoperated upon successfully.

Spoto reviews and compares the operative methods and results of other authors to those obtained from the Labhardt series.

For designation of the various stages of estrus and diestrus, in relation to the cyclic changes in the vagina, we have adopted Sjövall's classification, which of course is a modification of the classification set forth by Stockard and Papanicolaou. Estrus is divided into three stages, namely, I, II, and III. Diestrus is called Stage IV, and proestrus is symbolized as V. Stage I, or early estrus, is further subdivided into Ia, Ib, and Ic, according to well-defined histologic findings. The stages may be summarized as follows, according to findings in the vaginal smear:

- Ia: Intact mucous cells with intact nuclei. No evidence of degeneration.
- Ib: Vacuolated mucous cells with pyknotic or fragmented nuclei.
- Ic: Anuclear cells.
- II: Cornified nucleated cells.
- III: Flattened epithelial cells and *leucocytes*.
- IV: Leucocytes and occasional epithelial cells.
- V: Intact mucous cells and leucocytes.

Gross Changes

During diestrus, very little secretion is present in the vagina and cervix. The entire genital tract is relatively atrophic. In proestrus and early estrus, there is an abundance of tenacious mucus in the vagina and lower cervix. This changes to a thinner consistency in late estrus and is associated with many small white clumps, made up of cells. The genital structures undergo gross hypertrophy associated with evident softening and congestion.

Histologic Changes

Rather profound and characteristic alterations are noticed in the cervix. During diestrus, Stage IV, the lower portion of the cervix is comprised of a relatively thin mucosa, composed of two layers, the deeper portion consisting of several layers of squamous epithelium, sometimes designated as the basal layer. Covering the latter, is another layer made up of one or more rows of cuboidal or columnar mucus-containing cells, with dark-staining basal nuclei. The relatively few folds of epithelium present during this stage are short and blunt. Several leucocytes are usually noted in the epithelium and on the surface. The upper cervix discloses relatively simple glands, lined by low columnar or cuboidal cells containing a small amount of mucus, and compact dark-staining nuclei, which are usually basally situated. A few scattered leucocytes are usually present. Practically no secretion is encountered during this stage. Usually many vacuolated areas are present in the epithelium. The vaginal mucosa presents a picture very similar to the lower portion of the cervix. The uterus during this stage consists of a rather atrophic layer of endometrium and a dense compact stroma, with scattered leucocytes.

A very marked change occurs from about the fifteenth to the seventeenth day of the cycle. During this proestrus stage (Stage V), conspicuous evidence of proliferation is present. The basal epithelium of the lower cervix shows marked hyperplasia with many mitotic figures present in the deeper layers. Hyperplasia of the mucous layer occurs to a very marked extent while the cells fill up with mucus and actively secrete the substance in the lumen. There are many areas present where it appears as if the basal epithelium has become trabeculated, and here one gains the impression that a transition of the epithelium is occurring,

is present, covering plump and somewhat edematous folds. A regenerating epithelium is also noted. From the simple cuboidal epithelium a single layer of columnar epithelium develops, beginning during diestrus and remaining until proestrus.

In a most comprehensive work, covering a large series of investigative studies in the guinea pig and human subject, Sjövall¹² has arrived at the definite conclusion, that a clear-cut cyclic phenomenon is present in the cervix. In studying the cyclic changes in the human being, Sjövall found that, during the menstrual cycle, rhythmic changes were evident. During the proliferative phase of the endometrium, an increasing proliferation of the cervical epithelium takes place. Due to a considerable increase in the number of papillary excrescences, the contour of the superficial epithelium and the glandular epithelium becomes more and more irregular. The proliferation reaches its peak at the time of ovulation and thereafter diminishes, finally ceasing at the end of the secretory phase. The proliferative phenomenon is not seen shortly before, during, and after menstruation.

In Sjövall's series of 52 guinea pigs, he noted a very definite cycle, characterized by distinguishable histologic alterations in the cervix, which were coordinate in most cases with the cyclic variations in the vaginal mucosa and endometrium. Following a modification of the classification of Stockard and Papanicolaou,¹³ he divided the estrus cycle into five phases, with a subdivision of Stage I into three parts. He concluded that shortly before and during estrus, marked proliferation with abundant formation of folds took place. A great increase in the number of mucus-secreting cells and an increase in secretion of mucus occurred in the cervix. In the lower portion of this structure, proliferation of an epithelial layer situated beneath the mucous layer, was noted. Cornification and desquamation also were evident. At the end of the estrus phase, leucocytes migrated through the mucous membrane, and soon this layer reverted to an indifferent type, with low epithelium, which was characteristic of the diestrus phase. In the upper portion of the cervix, the changes were not as characteristic and no evidence of desquamation was noted.

Material*

Normally cycling animals were used in this investigation. Carefully selected virgin female guinea pigs were followed from one to three months after maturity had been reached. Fifty-three animals were used for this study. Vaginal smears were taken during various stages of the cycle by means of a wire loop moistened in normal saline solution. The vaginal smear was stained with hematoxylin and eosin, after being air-dried. Although the Shorr stain was tried, there was no particular advantage in its use. Animals were sacrificed at various stages, the genital organs immediately removed and fixed in 10 per cent formalin, Bouin's solution, or 100 per cent alcohol. Longitudinal sections or several transverse sections were made of the vagina, cervix, uterus, and ovaries, blocked in paraffin, sectioned, and then stained with hematoxylin-eosin, Best's carmine stain, or mucicarmine.

*The author wishes to express his gratitude to the Department of Pathology, University of Michigan Medical School for the preparation of the slides used in this work, and to thank Dr. R. C. Wanstrom, Associate Professor of Pathology, for her kind aid in their interpretation.

Proliferation continues in Stage Ib. The mucous cells which continue to be cast off from the vaginal mucosa, have undergone degenerative changes, such as vacuolization of the cytoplasm, and fragmentation of the nuclei. Cornification also shows some increase. In the lower cervix, the mucous cell layer has assumed rather marked proportions by virtue of an increase in the number of layers, and by exaggeration of the tufts and folds. Many cells have become separated and cast off into the lumen.

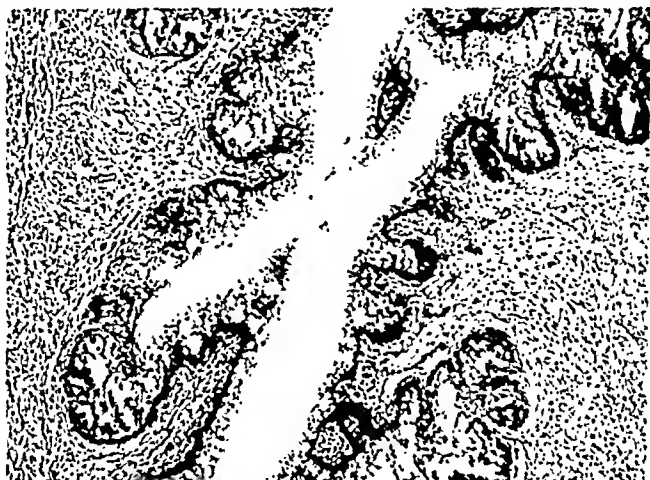


Fig. 2.—Low power photograph of lower part of cervix during Stage V (proestrus).



Fig. 3.—Low power view of upper cervix, Stage V (proestrus), showing simple glands.

The basal layer remains hyperplastic although mitotic shapes are no longer in evidence. The glands in the upper cervix are now tremendously enlarged with multiple tufts and excrecences. The cells are very tall and protuberant, with active secretion well marked. The growth is so great in many cases that the glandular lumina are filled by the volume of the cells. The endometrium is similar to that noted in Stage Ia.

During Stage Ic, cornification reaches its peak in the vagina and cervix, with desquamation of the anuclear cornified cells. The lower cervix shows considerable increase in the prominence of the cornified

from squamous-like cells to mucous cells. In the cranial portion of the cervix, the glands gradually enlarge and evidence of beginning fold formation and tufting can be seen. The cells have changed from euboidal to columnar and now contain basal nuclei and an increased amount of mucus. A small amount of this material can be noted within the glands themselves.

An equally intense change occurs in the vagina during Stage V. The squamous epithelium proliferates rapidly, showing mitotic figures in the deeper layers, and cornification in the upper layers. The covering layer of mucous cells undergoes marked hyperplasia and fold formation. The endometrium shows a corresponding hyperplasia and hypertrophy, although not as striking as in the cervix and vagina.

During the earlier part of estrus, the process is a continuation of the marked proliferative changes noted in the proestrus phase. In Stage Ia, the lower cervix follows closely the development of the vagina. Hyperplasia of the basal layer continues here with mitotic figures readily found. The mucous layer rapidly proliferates covering the basal layer.

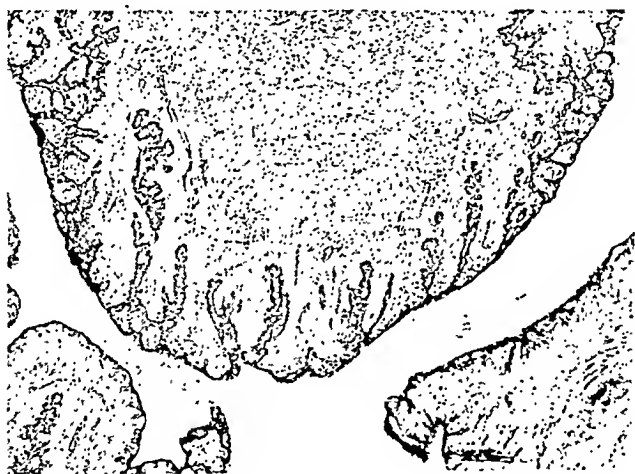


Fig. 1.—Low power photograph of lower portion of cervix and vagina during Stage IV (diestrus). Note thin mucosa.

In some areas there occurs a piling up of the mucous cells with beginning tuft formation. No evidence of desquamation is encountered, but active secretion makes its appearance. Leucocytes are conspicuously absent. In the upper cervix the glands have shown an increase in size and complexity, and active secretion is present. The cells are quite tall, many are tremendously ballooned out, due to the rapid increase in the amount of intracellular mucus. The darkly stained round nuclei are situated close to the base of the cell. Tufting has become more conspicuous. The vaginal mucosa becomes thicker, a marked hyperplasia of the epithelium occurs with mitotic figures still prevalent. Cornification in the upper layer, is much better developed than in proestrus. The mucous cell layer is quite thick, with many desquamated mucous cells present in the lumen. These cells contain well-formed small dark intact nuclei and show no evidence of degeneration. A very characteristic difference between proestrus and Stage Ia is the disappearance of leucocytes in the latter stage. The endometrium also shows alterations, the endometrial cells have become taller, and numerous mitotic figures are to be found. Practically no white blood cells are present. The stroma shows proliferation and edema.

tain variable amounts of mucus. A rather striking change now occurs in the position of the nuclei of the mucous cells. Hitherto, they were flattened against the base of the cell, but now they show a distinct tendency to be centrally situated. Many cells had shown this tendency in earlier phases, but the change is more pronounced during this stage.



Fig. 6.—Lower cervix (low power) demonstrating desquamation of mucous cells. Layer of cornification between the basal cell and mucous cell layers is quite evident.



Fig. 7.—Complex glands with tuft formation, noted in upper cervix during Stage Ic (low power).

Occasional formation of vacuolated spaces is encountered, but this is by no means characteristic. The vaginal mucosa is somewhat thinner, since the mucous cells and cornified layer have for the most part been cast off. The top layer of the epithelium consists of flattened or round cells, many of which have been cast off and are found in the lumen. The endometrium shows practically no change in cellular appearance, with the exception of leucocytic infiltration beneath the epithelium and in the glands.

Following ovulation, Stage III, or late estrus, is ushered in. The vaginal smear consists of flattened cornified cells plus leucocytes. The

layer. Here there is a casting off of the mucus and also the anuclear cells, but no further hyperplasia is noted. The glands have very much the same appearance as in Stage Ib. No significant alteration has occurred in the endometrium, other than that already noted in Stages Ia and Ib.

Stage II, according to Sjövall and others, is the interval immediately preceding ovulation. Examination of the smear reveals well-outlined round, polyhedral, or occasionally, some flattened cells with distinct but



Fig. 4.—Lower portion of cervix during Stage Ia. Note hyperplasia of basal layer and mucous cell layer (low power).



Fig. 5.—Stage Ib showing lower portion of cervix with marked hyperplasia of epithelial layers (low power).

pale intact nuclei. No leucocytes are present. In the lower cervix, distinct desquamatory changes occur, which are more impressive than in previous stages. Usually there is a separation between the mucous cell layer and the first or second layer of the basal cells, so that the desquamated cells consist of mucous cells plus basal cells. Leucocytes again are absent. In a few animals early degenerative changes may be noted in the epithelium, but this is not the rule. In the upper cervix, the glands are still quite irregular, show considerable tufting, and con-

The rather irregular glands of the upper cervix show active secretion, although diminished in amount in comparison to that noted in the previous stages. The nuclei for the most part are still centrally located. Degenerative changes and leucocytes, although present, are not nearly as great as in the lower cervix. However, the vacuolated areas are quite impressive. The vaginal mucosa is much attenuated and only a few layers of epithelium still persist. The upper layer consists of flattened cells, and throughout the tissue many white blood cells have made their appearance, with the greatest concentration toward the lumen surface. The endometrium shows a further increase in the number of leucocytes. Degenerative changes are quite conspicuous as evidenced by loss of cell detail and nuclear degeneration. A few cases showed areas of hemorrhage, although this was by no means the rule. From this phase there is a fairly rapid degeneration and the full picture of Stage IV is then encountered.

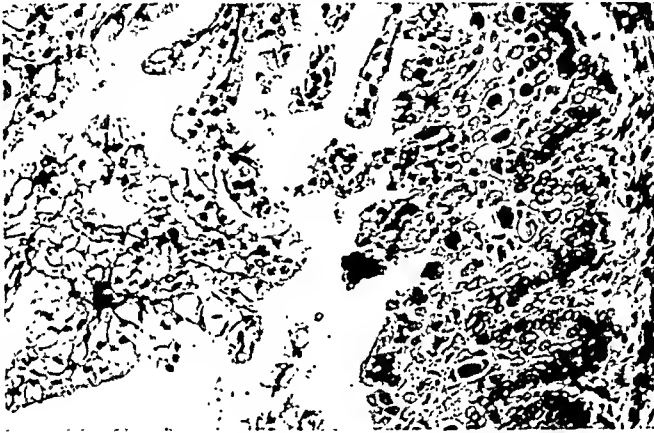


Fig. 10.—Marked degeneration in the lower cervix in Stage III (late estrus). Note the vacuoles containing the degenerated epithelial cells (high power.)

Comment

While the cyclic changes just described represent the characteristic picture, as in all biologic phenomena, variations from the "normal" were encountered. In this series, the length of the cycle varied from fifteen to eighteen days. The duration of estrus as determined by the opening and closing of the vagina, varied from two to four days. Stages I, II, and III did not bear a direct relation to the corresponding three days of the average estrus phase. By examining Table I, it is noted that most of the animals, presenting Stage III, were found in this phase on the second day of estrus. Seven guinea pigs showed the lack of complete correspondence of the stages in the various parts of the genital tract. Two more showed variation of the endometrium only, thus making a total of nine in this series which did not show characteristic coordinated alterations.

Considerable variation in the number and distribution of leucocytes in late estrus was noted. Some of this was undoubtedly due to the

characteristic changes noted in this phase are degeneration and leucocytic infiltration. The basal epithelium of the cervix is thinner than in previous stages of estrus. Many vacuolated areas are present in both the basal and mucous cell layers. Throughout the basal layer, many of the cells undergo a peculiar degenerative change. The cells become quite large, in fact many appear like giant cells. The cytoplasm changes



Fig. 8.—Low power photograph of lower cervix during Stage II (midestrus) illustrating desquamation of basal cells.

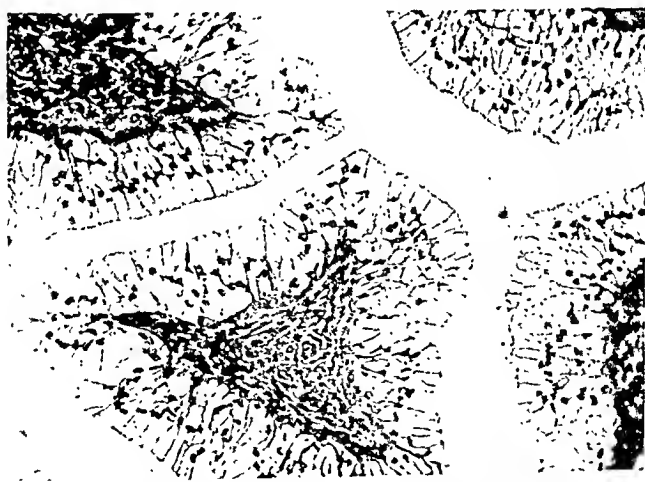


Fig. 9.—High power photograph showing centrally situated nuclei of the mucous cells in the upper cervix, during Stage II.

its staining properties, taking on a pinkish or orange color, while the nuclei become fragmented. Soon an area about these cells becomes vacuolated, and often the degenerated cells completely disappear, leaving spaces. Sjövall has not mentioned this degeneration of the cells, which we noted as a very constant and conspicuous change. Later, due to the great number of these vacuoles, the mucosa takes on a "punched-out" appearance. In some areas where degeneration seems to be at its peak, actual necrosis is seen. The leucocytes increase in number and are scattered throughout the basal and mucous cell layers.

evidence of proliferation in early diestrus, this being particularly true in the endometrium. In this series, the number of animals encountered in each stage is shown in Table II.

TABLE II

STAGES	NO. OF ANIMALS
Ia	8
Ib	2
Ic	2
II	6
III	12
IV	10
V	4
Inconclusive	9
Total	53

Our sections stained for glycogen were a keen disappointment. We expected to find a cyclic variation in respect to the glycogen content of the epithelial cells, but very little of this material could be demonstrated.

Although the most characteristic changes during the cycle were found in the cervical mucosa, there was a notable cyclic alteration in the stroma and blood vessels. During diestrus, the stroma is quite dense, with no evidence of congestion. There is an increase in both stroma cells and in the degree of vascularity in proestrus. This congestion and stromatous increase reaches its peak during early estrus with moderate edema also conspicuous at this time. These changes begin to show a definite decrease beginning with late estrus.

Sjövall did not detail the time of migration of the nuclei to a central location in the mucous cells, although we found this to occur with a high degree of consistency, namely during Stages Ic and II. This central location of the nuclei continues in Stage III, and often persists into early diestrus.

During Stage III, Sjövall stated that many leucocytes appeared in the epithelium of the cervix, as large round bodies. Leucocytes invariably do make their appearance during this phase, but we believe that the large round bodies, described by Sjövall as leucocytes, are actually degenerated epithelial cells. Some of the animals showed localized areas of simple necrosis, a further evidence of profound degenerative changes.

Summary

In our series, we have satisfied ourselves that in the guinea pig, a definite recognizable cyclic change occurs in the cervix, during the estrus cycle. These alterations follow very closely the variations present in the other parts of the genital tract, especially in the vagina. Emphasis must be placed on the fact, that the most characteristic findings are present in the lower cervix, although they are by no means

period in Stage III when the animal was sacrificed. For instance, in the early part of this stage, relatively few white blood cells are present, while later in the same phase more leucocytes are evident in the tissues. Occasionally, a few leucocytes persist in Stage Ia. Two animals showed

TABLE I

NO.	DAY KILLED	VAGINAL SMEAR (STAGE)	VAGINA (STAGE)	CERVIX (STAGE)	UTERUS (STAGE)
1	Second day estrus	II	II	II	II
2	?	III	III	III	III
3	First day estrus	III	III	III	III
4	Second day estrus	Ic	Ic	Ic	II
5	First day estrus	Ib	Ib	Ib	I
6	First day after estrus	Closed	IV	IV	IV
7	First day after estrus	Closed	IV	IV	IV
8	Second day estrus	III	III	III	III
9	Second day estrus	III	III	III	III
10	Second day diestrus	Closed	IV	IV	IV
11	First day estrus	II	II	II	III
12	Third day diestrus	IV	IV	IV	IV
13	?	Closed	IV	IV	IV
14	Eighth day diestrus	Closed	IV	IV	IV
15	Second day estrus	III	III	III	III
16	10th day diestrus	Closed	IV	IV	IV
17	Seventeenth day (proestrus)	V	V	V	III
18	First day estrus	Ia	Ia	Ia	I
19	Fifteenth day (proestrus)	V	V	V	V
20	Second day estrus	Ic	Ic	Ic	I
21	Fifteenth day (proestrus)	V	V	V	V
22	Second day estrus	III	III	III	III
23	First day estrus	Ib	Ib	Ib	I
24	Fifteenth day (proestrus)	V	V	V	V
25	Fifteenth day (proestrus)	V	Ia	V	V
26	First day estrus	Ia	Ia	Ia	I
27	Second day estrus	II	II	III	III
28	Second day estrus	II	II	II	II
29	Second day estrus	II	Ib	Ib	I
30	Sixteenth day (proestrus)	V	II	II	I
31	First day estrus	Ia	Ia	Ia	I
32	Second day estrus	III	III	III	III
33	First day estrus	Ia	Ia	Ia	I
34	First day estrus	Ia	Ia	Ia	I
35	First day estrus	II	II	II	II
36	Third day estrus	III	III	III	III
37	Second day estrus	III	III	III	III
38	First day estrus	V	V	V	V
39	Second day estrus	Ic	Ic	Ic	I
40	Third day estrus	III	III	III	III
41	First day estrus	Ia	Ia	Ia	I
42	Second day estrus	III	III	III	III
43	First day estrus	Ib	Ic	?	I
44	First day estrus	Ia	Ia	Ia	I
45	Second day estrus	III	III	III	III
46	Eleventh day diestrus	Closed	IV	IV	IV
47	Second day estrus	III	Ib	III	III
48	First day estrus	Ia	Ia	Ia	I
49	Second day estrus	II	II	II	II
50	Second day estrus	II	II	II	II
51	Eleventh day diestrus	IV	IV	IV	IV
52	First day diestrus	IV	IV	IV	IV
53	Second day estrus	II	II	II	II

In a series of 53 animals, 44 showed changes in the cervix which were coordinate with the normal rhythmic alterations found elsewhere in the genital tract.

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CEREBRAL COMPLICATIONS OCCURRING IN THE TOXEMIAS OF PREGNANCY*

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THE purpose of this presentation is to emphasize and illustrate some of the serious cerebral complications associated with the toxemias of pregnancy. During a four-year period of study from July 1, 1938, to July 1, 1942, there were 9,693 admissions to the obstetric service; 8,457 patients were delivered, and 1,009 mothers showed clinical evidence of late toxemia of pregnancy. In the group with toxemia, 41 patients had typical eclamptic convulsions; 6 patients developed critical cerebral complications, and there were 7 maternal deaths.

A clinical classification and the maternal mortality rate for the different types of toxemia are given in Table I. In this study, the admission ratio was approximately five colored to one white patient. The common occurrence of hypertensive disease in Negro women probably accounted, in part, for the high percentage of patients with chronic cardiovascular-renal disease complicated by pregnancy. The one death in the group with chronic vascular nephritis was due to cerebral arteriosclerosis with multiple minute hemorrhages. Acute nephrosis following abruptio placentae and a blood transfusion reaction accounted for one

*Read at a meeting of the Washington Gynecological Society, October 24, 1942.

absent in the upper part. In spite of the fact that the ovaries were examined grossly and microscopically, no attempt was made to correlate ovulation and corpus luteum formation with variations in the cervix, because of the technical handicaps incidental to making serial sections of the ovaries. We found gross inspection of the ovaries inadequate for proper correlation. We feel that the cyclic changes are probably dependent on the hormonal cycle. Sjövall has shown this to be true in part, although he believed that all the variations could be explained on the basis of estrin alone.

We may summarize the findings in the cervix during the various stages as follows:

ESTRUS

Stage Ia.—Lower cervix: Hyperplasia of the basal epithelium and the mucous cell layer. Absence of white blood cells.

Upper cervix: Proliferation of the glandular epithelium and an increase in the complexity of the glands. Absence of leucocytes.

Stage Ib.—Lower cervix: Hyperplasia of both layers, with beginning desquamation of the mucous cells.

Upper cervix: Increase in the size of the glands, and further tufting of the glandular epithelium.

Stage Ic.—Lower cervix: Definite cornification. Further desquamation of mucous and anuclear cells.

Upper cervix: Similar to Stage Ib.

Stage II.—Lower cervix: Distinct desquamation of mucous cells and nucleated basal cells.

Upper cervix: Shifting of the nuclei of the epithelial cells toward the center of the cell.

Stage III.—Lower cervix: Leucocytic infiltration into the mucosa and lumen. Definite degenerative changes.

Upper cervix: Degenerative changes. Conspicuous central location of nuclei of glandular epithelial cells. White blood cell infiltration.

DIESTRUS

Stage IV.—Lower cervix: Persistent leucocytosis. Further degenerative changes. Atrophy of basal and mucous cells to the resting type (low columnar or cuboidal cells).

Upper cervix: Similar changes as noted in lower cervix. The glands are smaller, and the vacuoles are quite prominent in many cases.

PROESTRUS

Stage V.—Lower cervix: Evidence of proliferation of basal and mucous cells. Leucocytosis diminishes. Many mitotic figures are present in the basal epithelium.

Upper cervix: The glands become larger and slightly more irregular. Epithelial cells increase in size.

Conclusions

Evidence has been presented to show that a definite cycle with characteristic changes is present in the guinea pig cervix.

Washington of many women of childbearing age who are undergoing economic and social readjustments and who possibly are not obtaining sufficient prenatal care.

Vascular Changes in the Toxemias of Pregnancy

Knowledge of the cerebrovascular changes in the toxemias of pregnancy may lead to earlier recognition and the prevention of critical intracranial complications. These changes may be classified as follows: (1) arteriospasm, (2) cerebral edema, (3) thrombosis of cerebral vessels, (4) intracerebral hemorrhage due to rupture of cerebral vessels or to rupture of vessels of the choroid plexus, and (5) extracerebral (subarachnoid) hemorrhage.

The cause of arteriospasm in the toxemias of pregnancy is not known. Clinical manifestations of arteriospasm depend upon the cerebral vessels involved, the duration of the spasm, and the degree of tissue anoxia produced. The sequelae of arteriospasm are seldom permanent. If death occurs, it is difficult to demonstrate the cerebral pathology.

The same factors which cause edema elsewhere in the body of patients with toxemia of pregnancy give rise to cerebral edema. Edema of the brain may lead to convulsions, coma, paralysis, and in some instances to death. The outstanding post-mortem finding in cerebral edema is the "wet brain" of serous apoplexy.

Clinically, thrombosis of a cerebral vessel may be difficult to distinguish from an intracerebral hemorrhage which has not extended beyond the brain tissue. In both instances the spinal fluid will be clear. Thrombosis is more likely to occur in the patient who has chronic vascular disease of hypertensive or syphilitic origin.

Intracranial hemorrhage is a relatively frequent and extremely significant complication of eclampsia. Factors which may lead to rupture of cerebral vessels in the toxemias of pregnancy are: (1) Changes in arteriocapillary walls due to spasm, edema, and ischemia; (2) increased vascular tension associated with eclamptic convulsions; (3) the chronic vascular changes of persistent hypertension and of syphilis; and (4) congenital aneurysm. Grossly bloody spinal fluid is diagnostic of a hemorrhage which has either originated in the meninges or has extended from the brain into the ventricles or subarachnoid space. If the cerebral hemorrhage is sudden and extensive, all motor pathways may be blocked, preventing convulsions.

Literature

In the literature, cerebral complications of the toxemias of pregnancy have been described under various headings.

Eclampsia With Convulsions and Cerebral Hemorrhage.—In 1881, Schauta found cerebral hemorrhage in 10 out of 90 eclamptic patients at autopsy. Prutz, in 1892, stated that 3 out of 22 brains examined showed cerebral hemorrhage. Schmorl, in examining 73 cases of fatal

death. Of the four patients who died with eclampsia, two had typical convulsions, and all four showed gross evidence of cerebral hemorrhage.

TABLE I. CLINICAL CLASSIFICATION AND MATERNAL MORTALITY RATE IN 1,009 PATIENTS WITH TOXEMIA OF PREGNANCY

TYPE OF TOXEMIA	NUMBER OF PATIENTS	IN- CIDENCE PER CENT	MATERNAL MORTALITY	
			NO.	PER CENT
Hypertensive cardiovascular disease, mild	160	15.86	0	0
Hypertensive cardiovascular disease, severe	131	12.98	1	0.76
Chronic vascular nephritis	83	8.23	1	1.20
Chronic glomerulonephritis	5	0.50	0	0
Acute nephritis or acute nephrosis	1	0.10	1	100.00
Pre-eclampsia, mild	413	40.93	0	0
Pre-eclampsia, severe	175	17.34	1	0.57
Eclampsia*	41	4.06	4	9.75
Total	1,009	100.00	8	0.79

*Eclampsia with and without convulsions.

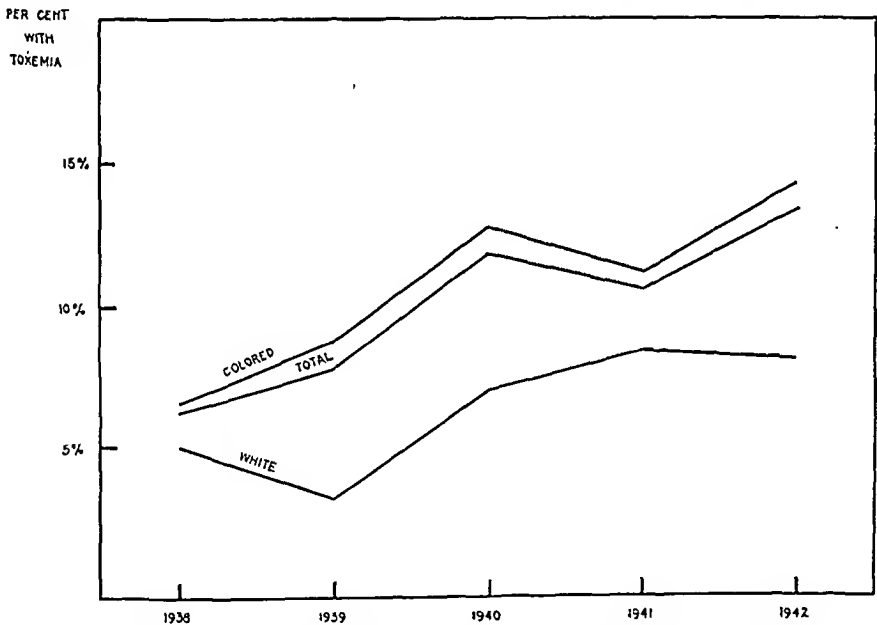


Fig. 1.—Incidence of toxemia occurring in the 9,693 patients hospitalized between July 1, 1938, and July 1, 1942.

In the two remaining cases, the cause of death was uncertain. One patient with severe hypertensive cardiovascular disease, uncontrolled diabetes, and premature labor died a few hours after admission of what was thought to be acute heart failure. The other patient went into labor with a severe preeclamptic toxemia. She died suddenly. The clinical impression was pulmonary embolism. Neither lumbar puncture nor post-mortem examinations were performed on these two patients. The presence or absence of cerebral hemorrhage as a factor in their sudden death was not determined.

During the past four years, the incidence of toxemia at Gallinger Municipal Hospital has increased from 6.52 per cent in 1938 to 13.43 per cent in 1942 (Fig. 1). The increasing incidence of toxemia in our group of patients may be partially explained by the recent migration to

The hospital course of this markedly edematous, moderately obese patient is outlined in Fig. 2. Because of fetal heart sounds and fetal activity, an immediate post-mortem cesarean section was performed.

Spinal fluid was grossly bloody in all specimens. Blood urea nitrogen was 20, uric acid 5.7, and sodium chloride 462 mg. per cent. Coffee-colored catheterized urine showed specific gravity 1.014, 4-plus albumin, white and red blood cells, and many granular casts. The coroner released the body without necropsy.

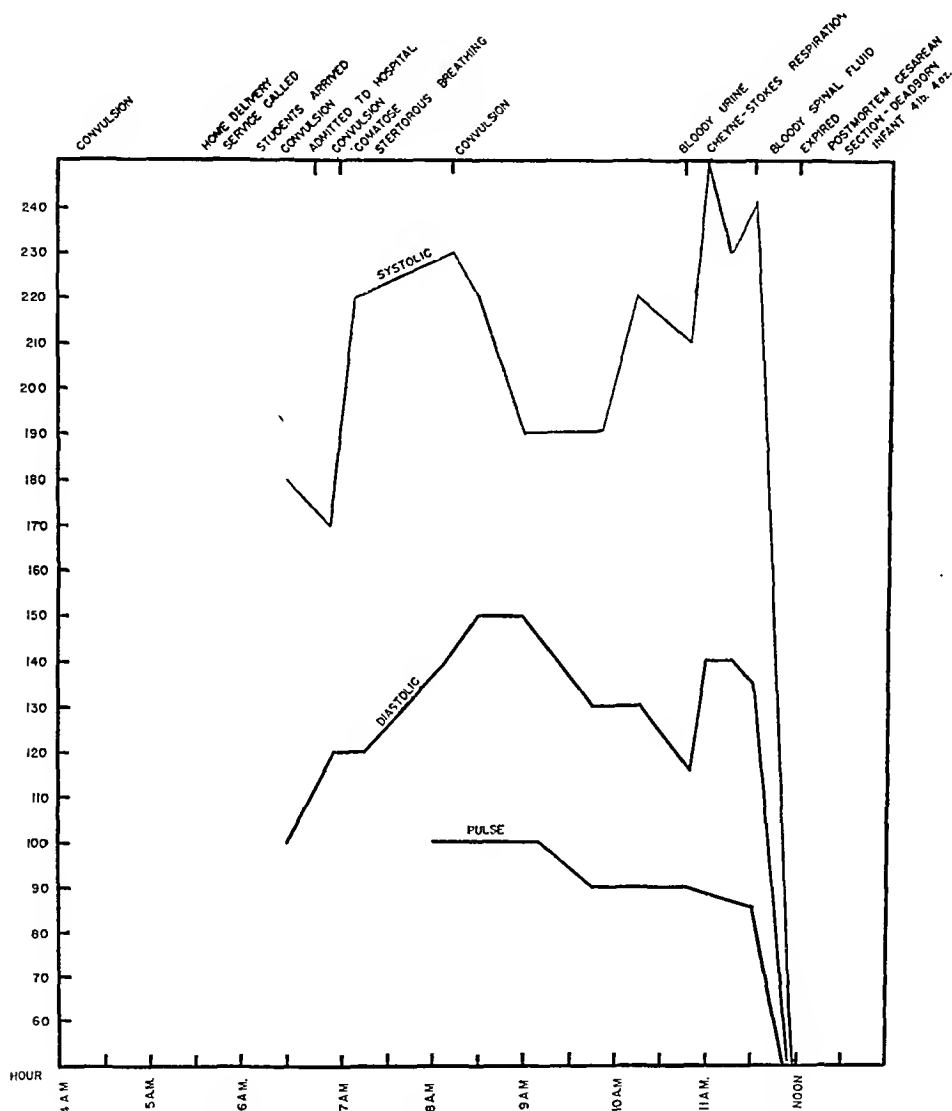


Fig. 2.—(Case 1.) Eclampsia with convulsions and cerebral hemorrhage.

CASE 2.—E. K., colored, gravida vi, 22 years of age, was admitted on Jan. 20, 1941, complaining of severe headache and amblyopia. At her only prenatal clinic visit, on Oct. 23, 1940, no symptoms or signs of toxemia were noted. About twenty-four hours after the report of a death in the family, the patient had two convulsions. Shortly after admission to the hospital, she had a third convulsion. Hourly blood pressure read-

eclampsia, found small pinhead-sized hemorrhages, or areas of necrosis in 58, and gross hemorrhage in only 1. Dieckmann states that Jaffe found 5 patients with massive cerebral hemorrhage in 8 autopsies and edema of the brain in the remaining 3. Rheindorf reported cerebral hemorrhage in 10 per cent of deaths due to eclampsia. Kosmak, in his monograph on toxemias, states that some degree of cerebral hemorrhage is found at autopsy in most eclamptic deaths.

Additional reports of cerebral hemorrhage in eclampsia have been recorded by the following authors: 7 cases by Meyer-Wirz, 5 by Bouffe de St. Blaise, 3 by Levant and Portes, 2 by Rheindorf, and 1 each by Weleh, Carver and Fairbairn, Maygrier and Chevane, Binder, Rhemann, and Liebers.

In 1887, Klebs reported gross hemorrhage of the brain occurring in a patient with acute yellow atrophy of the liver. In 1897, Pfannenstiel described an eclamptic death due to a ruptured cerebral varix.

Cerebral Hemorrhage in Eclampsia Without Convulsions.—In 1907, Slemons reported 9 cases (2 of his own) of eclampsia without convulsions terminating in cerebral apoplexy. In 1911, Schmid reviewed the literature and brought the total of reported cases to 24. In 1927, Caffier reviewed 38 cases. King reported a case of eclampsia without convulsions complicated by cerebral hemorrhage and analyzed 30 of the 44 cases previously reported. In 10 of the 30 cases, the diagnosis was missed until autopsy. Of 23 brains examined, 2 were normal, 2 were ischemic, 10 showed punctate hemorrhages, and 9 showed massive hemorrhage. In 1941, Abbott reported a patient with toxemia of pregnancy in which cerebral hemorrhage was diagnosed. The intracranial clot was removed on the second post-partum day. Except for a residual homonymous hemianopsia, the patient made a remarkable recovery.

Paralysis in the Toxemias of Pregnancy.—In 1904, v. Hoesslin made an extensive survey of all types of paralysis occurring in pregnant women. In his article he reviewed 32 cases of paralysis associated with the toxemias of pregnancy. Schwanen, in 1934, reviewed 47 cases which included those previously reported by v. Hoesslin, 12 additional cases from the literature, and 3 of his own. A search of the available literature revealed reports of additional cases of Bouffe de St. Blaise, Mondy, Cronson, Barrett and Harger, Liebieh, Henriet, Dieckmann, Hajkis, and McMann which were not included in Schwanen's article. McMann's report described an eclamptic patient who developed a monoplegia which lasted only five days and was attributed to arteriospasm. With the addition of a case to be presented below, 57 reports of paralysis in the toxemias of pregnancy are available for analysis. Forty-six patients had hemiplegia and 11 had monoplegia. There were 27 patients with and 30 without convulsions. In the entire group there were 20 deaths, giving a mortality rate of 35 per cent.

Eclampsia With Convulsions and Cerebral Hemorrhage

CASE 1.—L. T., colored, unregistered, gravida vii, aged 30 years, approximately thirty weeks pregnant, was admitted Aug. 5, 1941, in deep coma. Her first pregnancy terminated as an abortion. She subsequently gave birth to five living infants, each pregnancy being complicated by hypertension and albuminuria. For five weeks prior to admission, headache and edema of the extremities had been present.

sisted of one visit to a clinic on June 28, 1940, where it was recorded that she had had scarlet fever in childhood, blood pressure 180/110, and 1-plus albuminuria. Additional history of swollen ankles, seotomas, headache, and vertigo of one month's duration was obtained at the time of delivery.

The patient's terminal clinical course is charted from home delivery and hospital records in Fig. 3. Attention is called to the use of pituitrin in this hypertensive patient. Death occurred two and one-half hours after admission to the hospital.

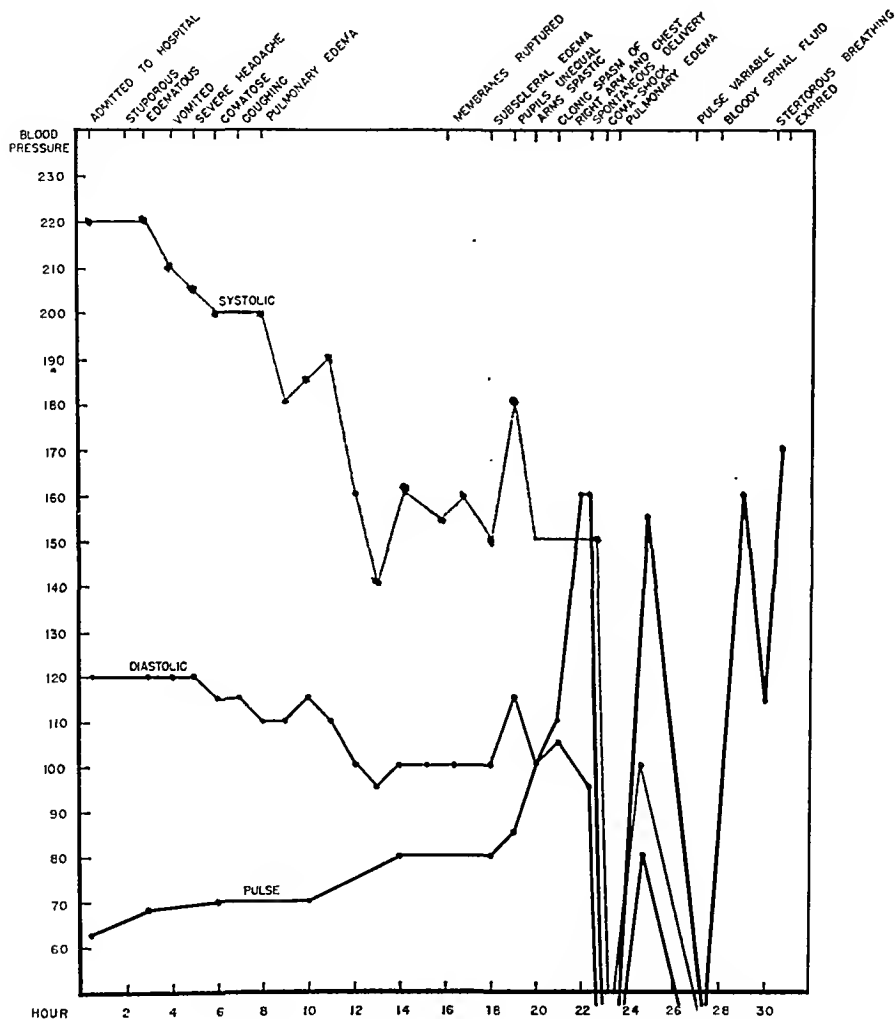


Fig. 4.—(Case 4.) Eclampsia with atypical convulsions and cerebral hemorrhage.

Spinal fluid was grossly bloody. Blood urea nitrogen was 20, cholesterol 200, and sodium chloride 511 mg. per cent. Urine showed 2-plus albumin, many red and white blood cells, and no casts. At post mortem, the enlarged liver showed diffuse subcapsular hemorrhage as well as gross and microscopic evidence of extensive periportal hemorrhage and necrosis. Hepatic hemorrhage was more pronounced in the right than in the left lobe. The kidneys showed edema and desquamation of the tubular epithelium. The glomeruli were normal. Unfortunately the brain was not examined.

ings showed the systolic blood pressure ranging between 130 and 180 and the diastolic pressure varying from 90 to 130 mm. Hg. Thirty hours after admission she delivered, spontaneously, a living infant weighing 5 pounds 13 ounces (2,637 Gm.). Following delivery, the pulse became slow and irregular. The blood pressure was maintained at a level of about 140/100. Ninety minutes after delivery, the patient became comatose; blood pressure dropped to imperceptibility, and the pulse became rapid and irregular. Pulmonary edema and gasping respirations developed. The eyes deviated to the left. The pupils became dilated, the right being larger than the left.

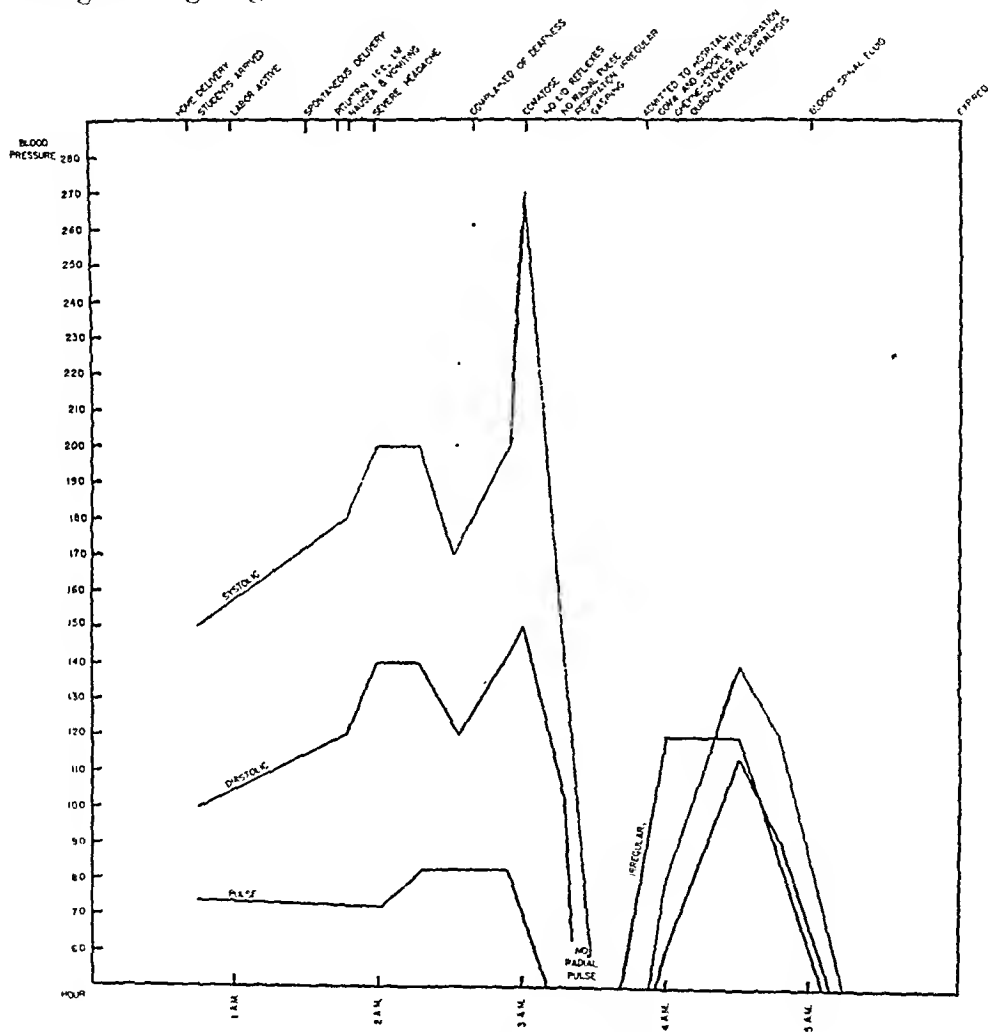


Fig. 3.—(Case 3.) Cerebral hemorrhage in eclampsia without convulsions.

Diagnostic lumbar puncture was productive of grossly bloody spinal fluid in all specimens. Patient died three hours after delivery. Urine showed 3-plus albumin and occasional casts. Permission for post-mortem examination was refused.

Cerebral Hemorrhage in Eclampsia Without Convulsions

CASE 3.—C. M., colored, gravida v, aged 27 years, was admitted from the home delivery service on July 3, 1940, in coma. Prenatal care con-

The meninges and formalin fixed sections of the brain failed to show gross softening or hemorrhage. All microscopic sections showed medial and intimal hyperplasia of the arterioles and preeapillaries. Congestion and small perivascular hemorrhages were present in the cerebellum and in the medulla beneath the floor of the fourth ventricle (Fig. 5). Death was attributed to advanced cerebral arteriosclerosis and multiple minute hemorrhages of the brain.

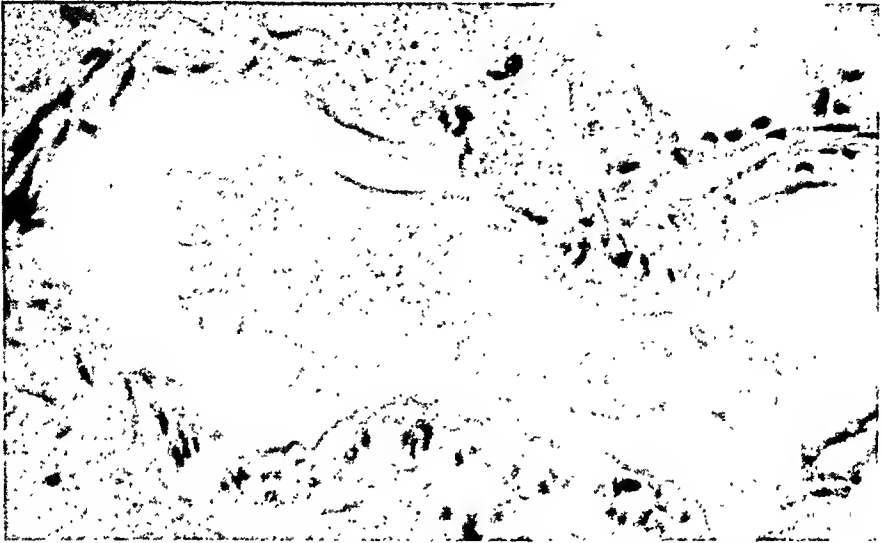


Fig. 5.—(Case 5.) Photomicrograph showing rupture of an arteriole in the medulla (high power).



Fig. 6.—(Case 6.) Eclampsia with convulsions and right hemiplegia.

Eclampsia With Atypical Convulsions and Cerebral Hemorrhage

CASE 4.—M. D., colored, unregistered, primipara, aged 25 years, in the twenty-sixth week of pregnancy, was admitted on Feb. 13, 1940, in active labor. Ankle edema had been present for one month. Headache and vomiting occurred on the day of admission. Her mother died in childbirth at 32 years of age. One brother died of cerebral hemorrhage.

The patient's clinical course is recorded in Fig. 4. In addition, ophthalmic examination showed perivascular edema of the left retina and old and recent hemorrhage into the right retina. The stillborn infant weighed 4 pounds 14 ounces (2,211 Gm.). The bloody spinal fluid was under a pressure of 47 mm. Hg.

Blood urea nitrogen was 29, cholesterol 166, icterus index 50, and sodium chloride 528 mg. per cent. Urine showed specific gravity 1.035, 4-plus albumin, hyaline and granular casts.

Important post-mortem findings were limited to the brain, liver, and kidneys. Upon removal of the dura, a flat mass of clotted blood covered both frontal and parietal areas. The right lateral ventricle was filled with a large, firm blood clot. Except for small blood clots in the arachnoid, the basilar portion of the brain appeared normal. Microscopic sections showed frank subarachnoid hemorrhage associated with petechial hemorrhage in the subjacent brain tissue. The liver showed many small areas of periportal focal necrosis. The kidneys showed cloudy swelling of the tubules and vascular congestion.

Pregnancy Complicated by Arteriosclerosis and Multiple Minute Cerebral Hemorrhages

CASE 5.—M. M., colored, gravida vi, para iii, aged 40 years, was admitted on Feb. 2, 1942, because of headache and hypertension complicating a pregnancy of twenty-six weeks' duration. Hypertension had been present with pregnancies in 1928, 1930, and after removal of a ruptured tubal pregnancy in 1941.

Important physical findings were: generalized edema, cardiac enlargement, and typical hypertensive changes in the optic fundi. Bi-daily blood pressure recordings ranged from 185/110 to 260/145.

On March 8, 1942, pregnancy was further complicated by partial premature separation of the placenta and a transverse presentation of the fetus. A living infant weighing 3 pounds 15½ ounces (1,800 Gm.) was delivered by classical cesarean section and local anesthesia. The first six post-partum days were uncomplicated. The blood pressure remained about 180/100. On the seventh day her temperature went to 101° F.; she complained of feeling faint, went into a short, generalized convulsion, and died suddenly.

Cerebrospinal fluid was clear. Blood urea nitrogen varied from 8.3 to 14, cholesterol 200, serum albumin 4.07, and serum globulin 2.57 mg. per cent. Urine showed a fixed specific gravity at 1.017, 2- to 4-plus albumin, hyaline, and granular casts.

At autopsy, significant findings were limited to the heart, kidneys, and brain. The heart weighed 525 Gm. and showed hypertrophy of both ventricles. No thrombi were found in any portion of the heart or pulmonary vessels. Coronaries were open in all of their main branches. Kidneys weighed 125 Gm. each, showed gross scarring of the cortical surfaces, and microscopic evidence of advanced arteriosclerosis. The liver showed no gross or microscopic evidence of hemorrhage.

Hypertensive cardiovascular renal disease, not peculiar to pregnancy, accounted for 37 per cent of the patients classified in this study. Coincidentally, this same group of patients contributed 37 per cent of the total maternal mortality in the toxemias of pregnancy. In addition, chronic hypertensive vascular disease preceded the development of toxemia and cerebral hemorrhage in three out of the four fatal cases of eclampsia reported above. From these data it is apparent that patients with hypertensive vascular renal disease are poor candidates for repeated pregnancies.

In the management of toxemias of pregnancy at Gallinger Municipal Hospital, a preliminary impression is made regarding the type of toxemia which the patient presents. *Treatment is directed at the predominating factors in the toxemia.* In pregnancy with hypertensive vascular disease, vasodilators and sedation are given. Care is taken not to overload the vascular system with hypertonic intravenous medication. In all toxemias there seems to be a definite contraindication to the use of pituitrin due to its vasopressor and antidiuretic effects. The second stage of labor is shortened by reasonable operative means, remembering that patients with toxemia withstand trauma very poorly. When possible, local is substituted for inhalation anesthesia.

In severe toxemias of pregnancy, attention should be focused on the manifestations reflected in the most vascular and vital of the body tissues, namely, the brain, liver, and kidneys. Cerebrovascular changes of arteriospasm and edema give rise to headaches, visual and auditory disturbances, convulsions, and paralysis. If these are recognized early and treated properly, intracranial hemorrhage may be prevented. Because of deep sedation, failure to perform a thorough neurological examination, transitory character of some paralyses, or in a few instances where massive intracerebral hemorrhage blocks all motor pathways, the physician may fail to recognize and localize important intracranial lesions. Thrombosis and rupture of cerebral vessels are evidence of late and serious changes in the toxemias of pregnancy. Although the prognosis is poor, early recognition and intelligent neurological treatment offer the pregnant patient with cerebral hemorrhage her only chance for recovery.

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Eclampsia With Convulsions and Hemiplegia

CASE 6.—L. G., white, primipara, aged 16 years, was admitted on Oct. 27, 1938, at term and in active labor. She had made one visit to a prenatal clinic on Sept. 12, 1938, where her blood pressure was recorded at 120/70. She had had scarlet fever at five years of age.

On admission the blood pressure was 200/140. Edema was generalized. Ophthalmoscopic examination revealed engorged veins, narrow, spastic arteries, and marked edema of the left disc and blurring of the right disc.

During the second stage of labor, the patient became extremely restless. With the aid of outlet forceps and ether anesthesia, she was delivered of a living infant weighing 6 pounds 5 ounces (2,863 Gm.). Her first eclamptic convulsion occurred at delivery. She had three additional convulsions at approximately one, two, and seven hours post partum. For forty-eight hours she remained semicomatose with a slow, irregular pulse, stertorous breathing, and a blood pressure which varied from 126/88 to 160/120. Sixty hours post partum the patient began to respond to questions, but was unable to speak. Her oropharynx was hyposensitive; tongue protruded to the right, and a flaccid paralysis of the right side of the body was present (Fig. 6). Spinal fluid was clear with no increase in pressure. When discharged from the hospital on the seventeenth post-partum day, she was able to walk alone. She had a right foot drop, a residual facial palsy, and some slurring of speech.

Blood urea nitrogen was 18, sodium chloride 576, serum albumin 2.38, serum globulin 2.19, calcium 13.3, and phosphorus 10 mg. per cent. Urine showed a specific gravity of 1.019, 4-plus albumin (Esbaech 13 Gm. per liter), hyaline and granular casts.

The consulting neurologists were of the opinion that eclampsia had been complicated by either thrombosis of, or hemorrhage from, the left middle cerebral artery in the Sylvian fissure.

We have been informed that this patient gave birth to a full-term infant on Dec. 29, 1939, at which time her blood pressure was normal and her only residual evidence of paralysis was a slight right foot drop.

Six patients representing the various types of serious intracranial complications occurring in the toxemias of pregnancy have been presented. In all six patients the spinal fluid and blood Kahn reactions were negative. Gross cerebral hemorrhage was present in four patients who died of eclampsia. One patient with chronic vascular nephritis died of multiple minute hemorrhages secondary to cerebral arteriosclerosis. One patient with eclampsia complicated by hemiplegia recovered.

Discussion

During the past four years, there has been an alarming increase in the toxemias occurring in pregnant patients admitted to Gallinger Municipal Hospital. All of the reasons for this recent rise in toxemia are not known. It is of immediate concern that 12 out of 41 patients with eclampsia had not even registered at a prenatal clinic. Only one (Case 5) of the six patients with toxemia and cerebral complications had received adequate prenatal care.

others with which the observations made in the present study do not agree.

Description of Senile Changes of the Fallopian Tubes

In many women nearing the menopause and in all after this time there develop certain changes in the Fallopian tubes. First of all, the connective tissue shows an increase in fibrillar elements, becomes relatively less cellular, and takes more and more the eosin stain. As a consequence of this connective tissue hypertrophy, the folds become broader and plumper and tend to lose their convolutions. The cyclically changing epithelium shows little or no alteration at this time. As sclerosis advances, the tube folds are largely obliterated until finally three to ten years after the menopause they appear as broad, fingerlike, stumpy elevations with only a few secondary folds. According to Tietze the elastic



Figs. 1, 2, and 3 are of the same magnification, and are all from the same portion of the outer third of the tube.

Fig. 1.—Normal Fallopian tube.

fibers entirely disappear except for a few to be found in the tube wall. With these more advanced changes in the connective tissue the epithelium has a loss of ciliated cells and a relative increase of nonciliated or secretory cells. Meanwhile, here and there in widening areas or patches there is a progressive diminution in height of the cells, resulting in an irregular level. Finally, six to ten years after the menopause the cells have become cuboidal, or almost flat in places, and without cilia so that there is eventually a resemblance to prepubertal epithelium.

Tietze pointed out that the effect of the connective tissue changes is more striking toward the distal end of the tube where folds are normally more numerous, slender, and long. This observation was confirmed by the examination of sections from various parts of a number of tubes.

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SCLEROSIS AND RELATED SENILE CHANGES OF THE FALLOPIAN TUBES

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IT WAS noted in the pathology laboratory of Harper Hospital that a large proportion of the cases with leiomyofibromas of the uterus also showed the sclerotic and other changes in the Fallopian tubes of middle and advanced age. Investigation of this relationship brought out several important points of interest.

The tube alterations accompanying the sexual climacteric, and therefore presumably due to ovarian deficiency, have received little attention in gynecologic literature. This is particularly true of this country. In fact, a rather thorough search of the recent literature failed to reveal in the English language any complete description of the changes. A partial exception to this statement is the article by Novak and Everett,¹ in which the epithelial changes are described, but the striking and earlier alterations of the apparently more sensitive connective tissue are largely passed over. Textbooks on gynecology, and even those dealing specifically with pathology, make very brief or no mention at all of the subject. In the foreign literature, however, there are a few good descriptions to be found. Of these, perhaps the most accurate is in the article by Tietze.² Consequently, the following brief description follows this paper closely, except for a few points not mentioned by Tietze, or

definite sclerosis. It is also noteworthy that occasionally there was some difference in degree of sclerosis for the two tubes from the same patient, but in no instance was it entirely lacking in a tube when definitely present on the other side. Novak and Everett state that the epithelial changes also show a variability in different parts of the tube. A point of minor interest is the fact that crowding together of the folds in advanced sclerosis is due not only to hypertrophy of the connective tissue but in part to the well-known shrinkage and diminution in the size of the tubes occurring in women nearing, at, and past the sexual climacteric. The accompanying microphotographs (Figs. 1, 2, and 3), which are the same magnification and from the same part of the distal third of the tubes, illustrate the marked alterations in the folds due to sclerosis and also indicate by the difference in the arc of the tube walls the shrinkage and lessening in caliber of tubes after the menopause.

It is noted that the above description is in accord with the intimation given before that the connective tissue changes are not only evidenced earlier than are those of the epithelium but are also more striking. Consequently, the tube changes can be referred to subsequently by the brief term of "sclerosis." The failure in the various parts of this paper to differentiate statistically between the grades or degrees of sclerosis is explained, of course, by the small numbers involved.

Sclerosis of the Fallopian Tubes in Cases With and Without Fibroids of the Uterus

As noted before, attention to this subject was attracted by the seeming high proportion of fibroid uteri with accompanying sclerosis of the tubes. To investigate this point, the hysterectomies at Harper Hospital beginning with Jan. 1, 1941, were reviewed until near the end of six months there were available 100 consecutive cases (approximately 46 per cent of the total number of 219 abdominal hysterectomies done during this time) selected to conform to the criteria given below.

1. One or more definite fibroids in the uterus 2 cm. or more in diameter. (This point was determined not only by the operative and gross pathology descriptions but also by a review of all the microscopic sections. In this way questionable cases and those with quite small leiomyofibromas were eliminated from the series.)

2. At least one Fallopian tube removed and available for study.

3. At least one ovary removed and available for study.

4. No old or recent salpingitis of a degree sufficient to distort the pathologic picture.

5. No evidence of pregnancy.

6. No radiation treatment more than six weeks previously.

Of these 100 cases the surprising number of 45 showed sclerosis of the Fallopian tubes varying from a slight, but definite, to a marked degree. In 7 others there was considerably more than a suggestion of the condition but still not sufficient to place them in the group with unquestionable changes. This high incidence of sclerosis with fibroids immediately introduced certain lines of speculation. For instance, since the changes are presumably due to ovarian deficiency, then here should be a potent

However, in every instance where a definite, even though slight, degree of sclerosis was present in any one section, it could be demonstrated elsewhere in the tube. The reverse also seemed true; that is, where one section is normal, the other parts of the tube likewise will fail to show

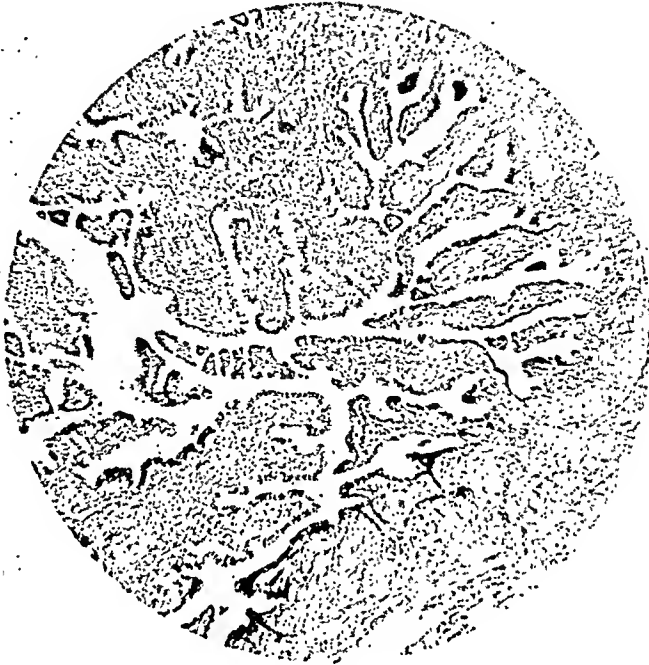


Fig. 2.—Moderate sclerosis of the Fallopian tube.



Fig. 3.—Advanced sclerosis of the Fallopian tube.

the fibroid cases and which, except for the carefully determined absence of leiomyofibromas of even the smallest size, corresponded to the same criteria employed in the selection of the first series. The close correspondence of Table III with Table II leaves little doubt that the high incidence of sclerosis of the tubes which at first seemed connected with the presence of fibroids was actually related in great part to the ages of the women. (Certain interesting incidental data brought out in assembling this second series are treated in another section of the paper.)

Relation of Previous Pregnancies to Sclerosis of the Fallopian Tubes

Although the data in the preceding section indicated that advancing age, with its endocrine derangements, was the principal factor in the senile changes of the Fallopian tubes, it seemed possible that other hormonal alterations might be found to play a part. For example, it was thought that the history regarding past pregnancies might give some information for or against an endocrine imbalance as a cause of tube sclerosis. All but 15 of the patients with fibroids, and of the 100 without these tumors all but 16, had a clear history relative to pregnancies. It was no surprise that fewer women of the first series (i.e., with fibroids) were known to have had pregnancies than was the case in the second. The difference, though, was not so great as often stated, being 55 as opposed to 66. Table IV shows rather remarkably similar occurrences of sclerosis of the tubes in women with and without previous pregnancies. Furthermore, essentially the same correspondence also holds when the cases are further split up into groups with and without fibroids of the uterus.

TABLE IV. INCIDENCE OF SCLEROSIS OF THE FALLOPIAN TUBES IN RESPECT TO A HISTORY OF PREVIOUS PREGNANCY, AND ALSO WITH AND WITHOUT FIBROIDS OF THE UTERUS. ONE SERIES OF 100 CASES WITH AND ANOTHER OF 100 WITHOUT FIBROIDS OF THE UTERUS

		WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTALS
Previous pregnancy	With fibroids	24	31	55
	Without fibroids	28	38	66
		52	69	121
No pregnancy	With fibroids	11	19	30
	Without fibroids	8	10	18
		19	29	48
Pregnancy uncertain	With fibroids	10	5	15
	Without fibroids	7	9	16
		17	14	31

It was thought that a determination of the lapse of time since the last pregnancy might perhaps give some lead as to the state of the endocrine gland balance with and without sclerosis. Unfortunately, in the relatively few instances among the two series of 100 each (with and without fibroids) which had an accurate history in this respect the last pregnancies in all but 2 cases had occurred five years or more before operation. This was considered too remote to convey any useful idea of the endocrine relationship to sclerosis of the tube.

Sclerosis of the Fallopian Tubes and Menstruation

The relationship of sclerosis of the Fallopian tubes to the menstrual history is shown in Table V. The two series of 100 each (with and

argument against a theoretical estrogenic excess as the cause of uterine leiomyofibromas. Again, the tube changes, or perhaps their cause, would offer some explanation for the higher incidence of infertility with fibroids and likewise the frequent futility of any and all treatment in these cases.

These and other conjectures offered reason for further investigation of the apparent high incidence of the tube changes associated with leiomyofibromas of the uterus. Considering the possibility that the size and mass of the tumors might have some influence on the tubes by pressure, by altering the circulation, or in some other way, the 100 cases were divided into groups graded according to the size of the uteri as compared to various periods in pregnancy. Although this is obviously a rough method of comparison, it should be sufficiently accurate to show any marked tendency even in this small series. Actually, as indicated in Table I, the incidence may possibly be some higher with the large tumors, but the differences are too slight to have any real meaning.

TABLE I. SIZE OF FIBROIDS AND SCLEROSIS OF TUBES

UTERI OF SIZE CORRESPONDING TO PREGNANCY	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
Up to 11 weeks	17	23	40
12 to 19 weeks	10	16	26
20 up to 23 weeks	7	8	15
24 weeks and over	11	8	19
	45	55	100

The investigation of age in relationship to sclerosis of the tubes was more successful (Table II). In fact, the differences were so striking as to suggest age, and not the presence of fibroids, as the likely factor of importance. To test out this idea, a comparison was made with a similar number of hysterectomy cases which fell into the same age groups as

TABLE II. WITH FIBROIDS. INCIDENCE OF SCLEROSIS OF FALLOPIAN TUBES ACCORDING TO AGES OF THE WOMEN

AGES	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
25-29	0	2	2
30-34	0	6	6
35-39	2	16	18
40-44	12	12	24
45-49	14	13	27
50-54	12	6	18
55 plus	5	0	5
	45	55	100

TABLE III. WITHOUT FIBROIDS. INCIDENCE OF SCLEROSIS OF FALLOPIAN TUBES ACCORDING TO AGES OF THE WOMEN

AGES	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
25-29	0	2	2
30-34	1	5	6
35-39	5	13	18
40-44	8	16	24
45-49	13	14	27
50-54	11	7	18
55 plus	5	0	5
	43	57	100

TABLE VI. RELATIONSHIP OF SCLEROSIS OF FALLOPIAN TUBES TO FEMALE SEX HORMONE ACTIVITY AS EVIDENCED BY HISTOLOGY OF OVARIES AND ENDOMETRIUM IN 200 CASES (100 WITH AND 100 WITHOUT FIBROIDS OF THE UTERUS)

	SCLEROSIS OF TUBES	NORMAL TUBES	TOTALS
Normal histology (corpus luteum, abundant follicles, cyclical endometrium)	43 (32%)	91 (68%)	134
Few primordial follicles	14 (54%)	12 (46%)	26
Senile ovaries	31 (78%)	9 (22%)	40
	88	112 (100%)	200

sex hormone activity, there is generally an increased incidence of senile changes in the Fallopian tubes. Also, a similar finding is the fairly large number of exceptions to the general tendency. Sclerosis of the tubes may, and often does, occur before there are histologic evidences of female sex gland failure. And, on the other hand, definitely senile appearing ovaries do not always have associated sclerosis of the tubes.

A combination of the data in Tables V and VI was calculated and might be of interest but was too complicated to be easily demonstrated in tabular form. However, the tendency was as could be expected; i.e., histologic evidences of normal hormone activity and associated normal tubes being usual with unchanged menstruation, less with anomalies of the periods, and rarely found after the menopause. Again, though, exceptions to the rule were present in practically all categories.

Sclerosis of the Fallopian Tubes and Sterility

Since sclerosis of the tubes develops with advanced sexual age and is presumably due to the ovarian hormone reduction or other endocrine alterations of that period of life, sterility should be a likely accompaniment of the condition. Moreover, the enlargement and crowding together of the tubal folds and also the loss of ciliated epithelium might well interfere mechanically with downward transportation of ova. In support of the expectation of barrenness in these cases, there was no instance of sclerosis of the Fallopian tubes associated with pregnancy found in the index files at Harper Hospital. As a check on this, an attempt was made to assemble 100 pregnancy cases with tubes available for study, which would fall into the same age groups as the two series of cases previously described. A review of the hundreds of operations for such conditions as ectopic pregnancy, cesarean section with salpingectomy, etc., during the last ten years quickly filled out the younger groups, but the older ones were largely or totally deficient. However, a comparison of this series (Table VII) with the other two (Tables II and III) indicates that, in spite of the inadequacy of the older groups, at least a few instances of sclerosis would have occurred in a similar series of non-pregnant patients. Actually, an examination of the microscopic sections showed that in the small series of pregnant women such was also the case, there being found one instance of rather slight but definite sclerosis and another with the condition moderately well advanced (Fig. 4). In both instances the pregnancy was in the tube.

Because of the incompleteness of this series, no accurate statistical conclusions can be drawn. Obviously, though, the fact that pregnancy was discovered at all is sufficient evidence that neither the condition itself nor its cause is an absolute barrier to fertilization of the ovum.

without fibroids of the uterus) were tabulated together since the numbers involved were small. It should be noted, however, that further justification for this was found in separate tabulations of the two series which were actually made but failed to show any significant differences between the two.

TABLE V. RELATIONSHIP OF SCLEROTIC CHANGES OF THE FALLOPIAN TUBES TO THE TYPE OF MENSTRUATION IN 200 PATIENTS (100 WITH AND 100 WITHOUT FIBROIDS OF THE UTERUS)

MENSTRUAL PERIODS	SCLEROSIS OF TUBES	NO SCLEROSIS
No change	15	48
Less (scantier or infrequent)	5	4
More (profuse or frequent)	44	55
None for 2 to 6 months	1	1
None for over 6 months	12	1
Bleeding after menopause	9	0
Menstruation not noted	2	3
	88	112

The data in Table V emphasize the general association of tubal sclerosis with sex hormone diminution and failure as evidenced by menstrual alterations and cessation. Where no menstrual changes were noted, there were relatively few instances of sclerosis of the tubes. Whereas, with disturbances in frequency or amount of the periods, about one-half of the patients had definite sclerosis of the tubes. And, after climacteric cessation of menstruation, the great majority of tubes were affected. Attention is particularly directed, however, to the exceptions in the general trend. These clearly indicate that sclerosis of the tubes has only a general correspondence to the menstrual history, sometimes preceding the menopause, but also in a few instances not yet appearing well after the climacteric.

Sclerosis of Fallopian Tubes and Histology of Ovary and Endometrium

A comparison of the occurrence of tubal sclerosis (in the two series of 100 each) with the presumable sex hormone status as indicated by the histology found in the ovary and endometrium is shown in Table VI. The presence, either alone or in combination, of a corpus luteum, a normal number of primordial and maturing follicles, or a definitely cyclical endometrium (late proliferative or secretory phases) was considered sufficient evidence to place a case in the normal gonadal division. Another group was made up of those with only an occasional follicle, which is sometimes the finding just before, at the time of, and for a few years after cessation of menstruation. And then came those with entire absence of follicles, or in other words senile ovaries. Since only one or two sections to each ovary were as a rule available for study, it is possible that a few of the cases in the last two groups, if more careful examinations were possible, actually should belong in the hormonally more active division. The most probable error in this table, then, would be in the direction of underestimating the number of more gonadally normal cases. Indeed, it might possibly be more correct to incorporate the second groups in the first ones. Actually, however, the numbers are small and so nearly equal that such a change would have no effect on the significance of the table.

The conclusions to be drawn from Table VI are essentially the same as those from Table V. With histologic evidences of diminution in female

fibromyomas, amounted to approximately 46 per cent of all the hysterectomies during a period of not quite six months. This percentage in itself, and without regard for additional fibroid cases not counted because of absence of tubes or ovaries, small size of fibromas, etc., is actually in excess of that reportedly found with and frequently believed to be significant in certain conditions, such as cancer of the body of the uterus, sterility, and pelvic inflammatory disease. Less definite, though perhaps equally impressive, were results obtained in the extensive search which was necessary for the collection of the 100 cases without fibroids. The 50 required for the age groups through forty-four years were secured from approximately 800 hysterectomies done during the year 1941 and most of 1940. For the older groups, however, it was necessary to go back, in addition, through 1939 and well into 1938 to find 50 suitable cases definitely without fibroids. This does not mean that all the remaining cases had fibroids. In fact, the majority were ruled out at the start on account of unsuitable age and without consideration of the presence or absence of uterine tumors; and others because of advanced pelvic inflammatory disease, pregnancy, or some other failure to conform to the criteria given before. In the cases remaining for study, however, a review of the operative records, the gross descriptions, and the microscopic sections showed considerably more than one-half with fibroids of appreciable size. Since in this part of the study an effort was made to select so far as possible cases with absolutely no leiomyofibromas, the remaining rejections were made in considerable part because of very tiny tumors. Obviously, in this last group the fibroids could not be considered "clinically significant," regardless of what may be meant by that very indefinite and variable and yet frequently used term. There is certainly the indication in these cases, however, that statistics involving fibroids of the uterus are likely to be meaningless unless the cases are selected in accord with definite standards regarding size of the tumors and other features, and unless comparison is made with control series.

In the literature there are also studies connecting fibroids and malignancy from the reverse point of view. For example, statements may be found to the effect that patients with fibromyomas of the uterus have a higher incidence of carcinoma of the uterine fundus than is the case in those without fibroids. This, if true, might be simply a reflection of the probable fact (at least so far as Harper Hospital is concerned) that on the average hysterectomy for fibroids is done later in life than for pelvic inflammatory disease and some other common indications. As a matter of fact, though, in the cases from Harper Hospital there was no instance of carcinoma involving the uterine body in the 100 fibroid uteri; whereas, in the other 100 without even small fibroids but which did correspond in age and other respects, there were 8 cases of fundus cancer. Results from these groups are admittedly far from trustworthy (because of small numbers and for other obvious reasons),

The question concerning the importance of either or both as a *relative* hindrance to pregnancy remains unanswered by this study. The same is true of the possible role of sclerosis as a cause of tubal pregnancy by mechanical obstruction to migration of the fertilized ovum through the Fallopian tube to the normal site of implantation in the uterus.

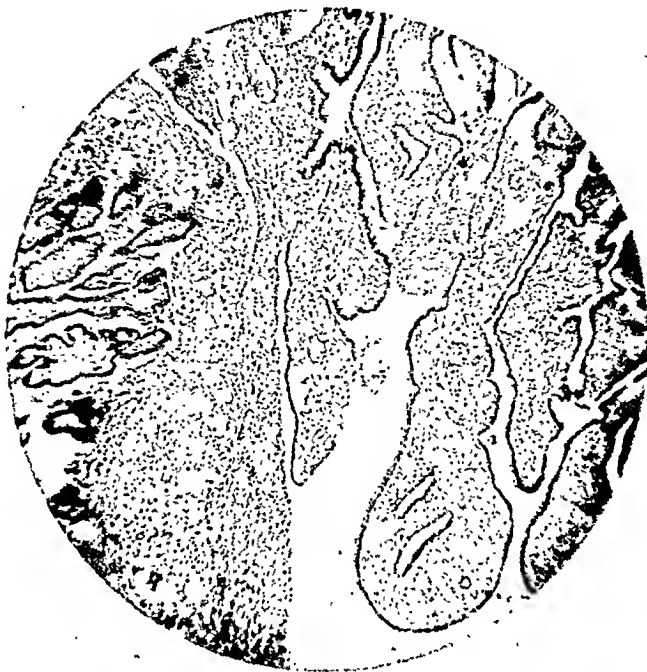


Fig. 4.—Moderately advanced sclerosis of the Fallopian tube associated with tubal pregnancy. The greatly enlarged and stumpy folds in the tube lumen on one side are separated by a partition from chorionic villi on the other.

TABLE VII. OCCURRENCE OF SCLEROSIS OF THE FALLOPIAN TUBES WITH PREGNANCY. (CASES INTENDED TO BE COMPARABLE IN AGES TO THE SERIES IN TABLES II AND III, BUT A REVIEW OF THE OPERATIONS FOR 10 YEARS FAILED TO FILL OUT THE OLDER GROUPS)

AGES	NO SCLEROSIS	WITH SCLEROSIS	TOTAL
25-29	2	0	2
30-34	6	0	6
35-39	17	1	18
40-44	12	1	13
45-49	—	—	0
50-54	—	—	0
55 plus	—	—	0
	37	2	39

Incidental But Important Points Suggested by the High Frequency of Leiomyofibromas in This Study

Not pertaining to the principal purpose of this study, but nevertheless of interest, were certain impressions derived from the indication of a generally high frequency of fibroids in the uteri removed at Harper Hospital. As previously stated, the first series of 100, or those with

A PRINCIPLE OF PHYSICS AS APPLICABLE TO SHOULDER DELIVERY*

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THE methods proposed for the extraction of the shoulders, as gathered from the current textbooks on obstetrics, are nearly uniform and do not differ materially from those taught a century or more ago. It is a fair criticism to state that not enough emphasis is given therein to the problem of the impaction of shoulders in its relation to the prevention of fetal death or lasting injury. In fact, both in teaching and in practice, it would appear that disaster attributable only to difficulty in shoulder delivery is to be accepted as an unavoidable incident.

Very few of our mechanical problems in obstetrics require emergency treatment. For example, if we have a persistent occipitoposterior position or a transverse arrest of the head, we usually have hours of warning and ample time in which, if necessary, to call in more expert help. Difficulty in the delivery of shoulders, however, usually comes as a complete surprise. We have no warning, a real emergency exists, and the minutes we have in which to make a safe delivery usually pass much faster than expert help can arrive.

It would not only be confusing, but it is unnecessary at this time to discuss the various shoulder presentations which may follow the delivery of the head. Instead, a simple, easily taught, working principle or plan will be presented, which can be applied to all shoulder problems.

This maneuver is based on a well-known law of physics applicable to the screw. A screw is a continuous spiral inclined plane, which when engaged in suitable threads is used where we wish to create the greatest resistance to its release by a direct pull. It follows, then, that a direct pull is the most difficult way to release a screw.

It will be demonstrated that a large baby in passing through a relatively small birth canal adapts, or must be made to adapt, the attitude of a screw, and that there are three "threads" in the female pelvis which prevent this large screwlike object from being released by a direct pull.

To illustrate this principle a wooden manikin has been constructed with shoulders so large that they cannot be delivered by a direct pull, or any textbook method. If, however, we maneuver it into the attitude of a screw it is just as easily released or unscrewed as a well-fitted

*Read at a meeting of the Section on Obstetrics and Gynecology of the New York Academy of Medicine, May 26, 1942.

but there is at least a strong suggestion here that properly comparable series might well revise the widespread impression that fibroids, or their etiologic factors, have a causal relationship to carcinoma of the uterus.

Summary

With advancing sexual age, the Fallopian tubes undergo certain changes consisting, first of all and most typically, of a marked hypertrophy and sclerosis involving the connective tissue of the folds. Later, there is also a replacement of ciliated epithelium by nonciliated and flatter cells. This sclerosis was noted in a high proportion (45 per cent) of cases with uterine leiomyofibromas. But the occurrence had little or no relationship to the size of the tumors. Moreover, an investigation of a like number of cases, which corresponded in all particulars except for the absence of even tiny fibroids, showed the condition in approximately the same proportion, the incidence increasing in both series with advancing age. Sclerosis of the Fallopian tubes showed no relationship to the history regarding previous pregnancies. The incidence of the condition was increased with the development of irregularities and anomalies of menstruation, and this was most marked with the onset of the climacteric and afterwards. The same tendency was noted also with the histologic evidences of sex hormone diminution. However, both here and with the menstrual changes there were definite exceptions to the general rules. Examination of a small series of tubes associated with pregnancy showed that sclerosis is occasionally present, and therefore it (or its cause) is not an absolute barrier to pregnancy. Left unanswered, however, were such questions as its possible role as a *relative* factor in sterility and also as a cause of tubal pregnancy. An interesting point incidental to the main purpose of this study was the discovery of such a high frequency of leiomyofibromas of the uterus in the material from Harper Hospital as to cast doubt on statistical studies which apparently indicate a relationship between fibroids and certain other conditions, particularly carcinoma of the uterine fundus.

The valuable advice and kind assistance of Dr. Plinn F. Morse, Pathologist at Harper Hospital, are gratefully acknowledged.

References

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Incidentally, this same principle of physics is applicable to most of our mechanical difficulties in the delivery of the head of a baby. A persistent occipitoposterior position, and transverse arrest, are two examples of "crossed threads." Most maneuvers have been devised to prevent or correct a "crossed thread" attitude of some part of the baby's body. A series of pictures (Figs. 1 to 16) is presented graph-

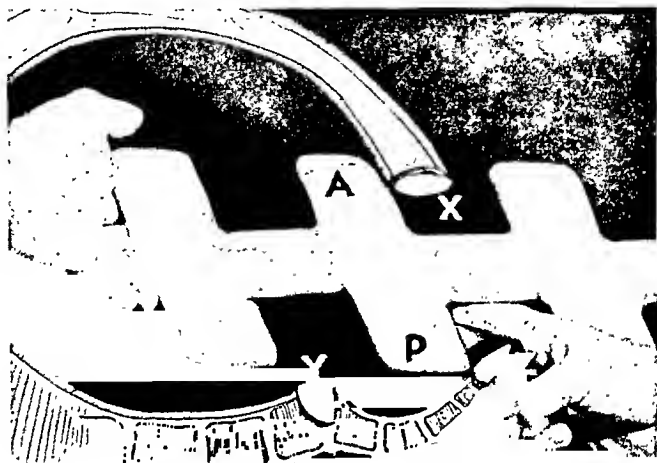


Fig. 3.

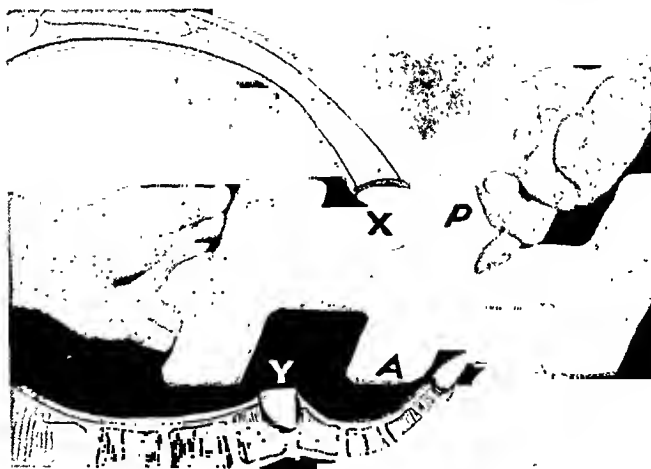


Fig. 4.

Figs. 3 and 4.—In these figures a longitudinal section of the maternal pelvis is superimposed upon these three threads, but does not in any way change or alter the mechanical principle involved. We still have three threads, X, Y, and Z, in exactly the same relative position, except that now we recognize them as the "pubic thread" X, the "promontory thread" Y, and the "coccyx thread" Z. The screwlike object cannot be released by pulling. It can be released only by turning.

screw cap is released from a bottle. But who has not had difficulty at times in releasing a screw from a bottle? The reason for this difficulty is always the same, a crossed thread. Unless we are able to correct the crossed thread attitude, we cannot without damage release a screw cap from a bottle. We cannot release safely the shoulders of a large baby with a "crossed thread" unless we are able to correct the crossed thread attitude.



Fig. 1.—This figure shows a longitudinal section of a wooden screw engaged in three threads, X, Y, and Z. Remembering the law of physics applicable to the screw we would waste no time in trying to disengage it by direct pull. It is immediately apparent that the only way it can be released from its retaining threads is by turning in the proper direction. Since it is a longitudinal section of a screw it has lost the advantage of the continuous spiral inclined plane, as a result of which it is necessary that the left hand produce a downward thrust synchronized with a lateral pressure with two fingers at P upward clockwise along the circumference of the arc to 12 o'clock.

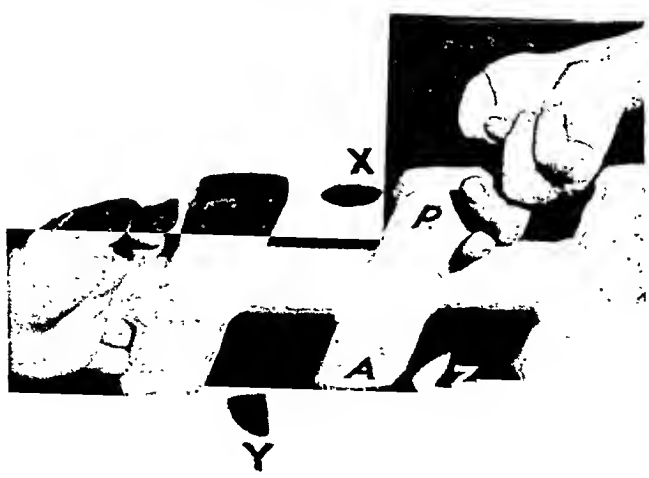


Fig. 2.—That part of the screw marked P has now been released from the threads X and Z. The part marked A has passed from its position behind thread X and now occupies the same position previously occupied by P. Repeating this procedure, A can be released in the same manner. So far the demonstration has been in strict accordance with the law of physics applicable to the screw. It cannot be released by a direct pull. It can be released only by turning.



Fig. 7.



Fig. 8.

Figs. 7 and 8.—This is an exact reproduction of a normal gynecoid pelvis made from plastic glass, so that by suitable lighting the various models can be watched as they pass through the pelvis. The three threads, "pubic thread" X, "promontory thread" Y, and the "coccyx thread" Z, interfere with the release of the second part of the wooden screw which corresponds to the shoulders. It cannot be released by *pulling*. If, however, precisely the same maneuver is used as that employed in releasing the wooden screw in Figs. 3 and 4, this rigid wooden screwlike object can easily be released from the actual pelvis.



Fig. 9.—(See opposite page for legend.)

ically to illustrate this maneuver. The legends beneath these pictures describe fully the principle and procedure, step by step.

Recapitulation of Technique

1. *In Vertex Presentation.*—A downward thrust is made with the left hand on the buttocks of the baby. At the same time two fingers of



Fig. 5.

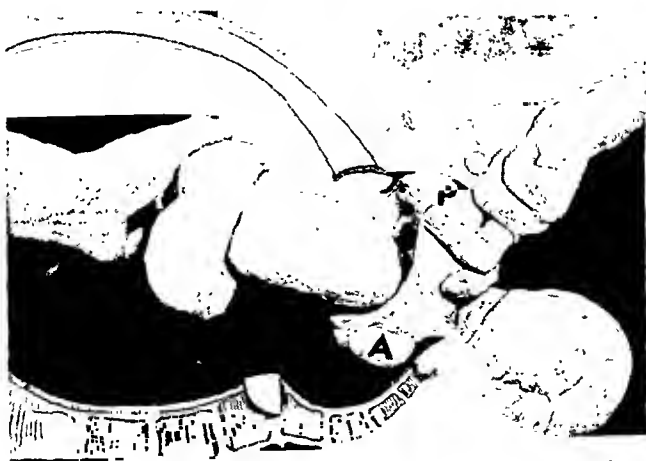


Fig. 6.

Figs. 5 and 6.—These figures show, engaged in these three threads, a wooden manikin with shoulders so large that they cannot be delivered by pulling. There is not enough room to force the hand under the "pubic thread" in an attempt to pull the anterior shoulder out. There is not enough room to force the hand into the crowded hollow of the sacrum. There is, however, ample room to insert two fingers between the baby's head and shoulder without touching the maternal parts except at the labia. A downward thrust is made with the left hand on the buttocks of the baby. At the same time two fingers of the right hand, on the anterior aspect of the posterior shoulder, make gentle clockwise pressure upward around the circumference of the arc to, and past, twelve o'clock. The posterior shoulder is now delivered.

and the remaining shoulder is delivered. Again the pressure was made away from the perineum. Sometimes it takes a little practice to get the pressure of the two hands properly synchronized. The turn cannot be made until the posterior shoulder has passed the spines.



Fig. 12.—The anterior shoulder has passed from its position behind the pubic bone through an arc of 180 degrees and now occupies precisely the same position previously occupied by the posterior shoulder. In passing from its position behind the pubic bone to the hollow of the sacrum it has exerted no pressure on the perineum. Two fingers are inserted between the baby's head and shoulder and are finally placed, as illustrated, on the anterior aspect of the remaining shoulder. With pressure applied downward from above with the left hand, the two fingers of the right hand make gentle counterclockwise pressure upward around the circumference of the arc to and past twelve o'clock, and the remaining shoulder is delivered.



Fig. 13.—Again the pressure was made away from the perineum. Sometimes it takes a little practice to get the pressure of the two hands properly synchronized. The turn cannot be made until the posterior shoulder has passed the spines.

the right hand, on the anterior aspect of the posterior shoulder, make gentle clockwise pressure upward around the circumference of the are to, and past, twelve o'clock. The posterior shoulder is now delivered.

With pressure applied downward from above with the left hand the two fingers of the right hand make gentle counter-clockwise pressure upward around the circumference of the are to and past twelve o'clock,



Fig. 10.

Figs. 9 and 10.—Fig. 9 shows what happens as a result of this pressure. The anterior shoulder is impeded in its downward progress by the "pubic thread." The "pubic thread," acting as a fulcrum, causes the posterior shoulder to descend into the hollow of the sacrum until it has passed the spines. As soon as the posterior shoulder has passed the spines, the two fingers of the right hand start making gentle clockwise pressure on the anterior aspect of the posterior shoulder upward around the circumference of the arc to and past twelve o'clock.

Fig. 10 illustrates the chief cause of failure when this maneuver is first attempted. Many operators try to turn the shoulders at this point. It is impossible. From a mechanical standpoint the shoulders are now in a position known as a crossed thread. It is just as impossible to turn shoulders with a "crossed thread" as it is to remove a screw cap from a bottle with a crossed thread. The next step is to correct this "crossed thread" attitude. The buttocks of the baby are firmly grasped with the left hand and slow gentle pressure is made toward the pelvis.

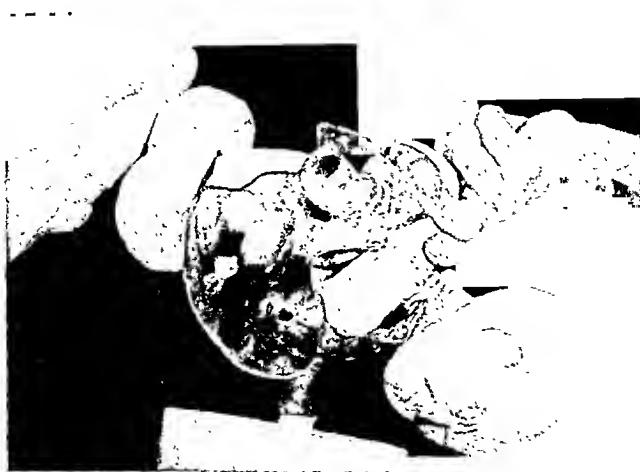


Fig. 11.—The posterior shoulder has now been delivered.



Fig. 16.—Illustrating the position of the operator at the side of the patient in performing this maneuver.

Summary

1. A wooden manikin, with shoulders too large to be delivered by pulling, is easily delivered according to a law of physics applicable to the screw.

2. If the shoulders of a wooden manikin are so large that they can be delivered in only one way, it would seem that this way would be the easiest, and therefore the least dangerous, way to deliver a live baby.

3. After the head has been born the shoulders of the baby resemble a longitudinal section of a screw engaged in three threads, the "pubic thread," the "promontory thread," and the "coccyx thread."

4. Any pulling on the baby's neck or axilla is mechanically incorrect because it violates a simple, well-known law of physics applicable to the screw.

5. There is no stretching of the trapezius muscle, and consequently no danger of injuring the cervical nerves.

6. The pressure is away from the perineum.

7. This maneuver cannot be performed unless the posterior shoulder has passed the spines.

8. Pressure from above, on the buttocks, must be applied by the operator (not an assistant) in order to synchronize the pressure of the two hands.

9. The passage of a baby through the birth canal is, in the vast majority of cases, an engineering problem. By applying a law of physics applicable to the screw, we find that most of our difficulty is due to a "crossed thread" or improper inclination of some part of our screwlike object. For example, extension of the arms, or nuchal arms, in a breech delivery may prevent the shoulders from adopting the proper inclination or screwlike attitude necessary for delivery. In the vertex presentation extension of the arms along the baby's body may interfere with the proper inclination of the shoulders. A Bandl's ring does the same thing.

2. *In Breech Presentation.*—The technique is identical with that for vertex presentation except that the expulsion force is applied by gentle traction on the legs instead of downward pressure on the buttock.

3. If the baby's back presents toward the right the turning is clockwise. If its back presents toward the left, the turning is counterclockwise.



Fig. 14.



Fig. 15.

Figs. 14 and 15.—Illustrating how the same mechanical principle is applied to the shoulders in the breech delivery. Gentle traction is made by pulling on the feet with the left hand. The anterior shoulder becomes impeded in its downward progress by the pubic bone. The pubic bone, acting as a fulcrum, causes the posterior shoulder to swing down into the hollow of the sacrum. After the posterior shoulder has passed the spines (it is impossible before) two fingers of the right hand make gentle clockwise pressure on the anterior aspect of the posterior shoulder upward around the circumference of the arc to twelve o'clock, and the posterior shoulder is easily delivered. The arm is now brought downward with a wiping motion across the chest, and it, too, is easily delivered. The remaining shoulder is delivered by making gentle counterclockwise pressure with two fingers of the left hand on the anterior aspect of the shoulder upward around the circumference of the arc to twelve o'clock. The arm is then brought downward across the chest.

appreciable trauma. The purpose of this paper is to present such a procedure, which has been used over a considerable period of time with reasonably good results.

A number of articles have appeared in the recent literature on the use of novocain as a local anesthetic in obstetric practice. The various methods of administration involved the sacral, epidural, parasacral or presacral approach. Some of the investigators reporting on this type of anesthesia employed it in routine deliveries, while others emphasized its value in various complications other than cervical dystocia.

Bickerstaff³ used sacral block anesthesia by means of low sacral injection of 2 or 3 per cent procaine in 55 routine deliveries, and in 10 cases where it was used solely for operative delivery or as expectant treatment of dystocia, preliminary to operative intervention. However, in addition to the many advantages of this method which he cites, he admits that obesity or sacral edema may render his procedure technically inapplicable. He adds: "It is difficult, even with considerable practice, to enter the sacral canal with the patient lying on her side, particularly with stout, flabby, overlying tissues, often edematous, sagging as much as an inch or more, and distorting the surface anatomy." Local skin lesions are, of course, another contraindication, as pointed out by the same author.

An easier method is that of pudendal nerve block by the presacral approach. But, as Waldman⁴ points out: "Since 1910 a number of papers have appeared in the literature advocating pudendal anesthesia, but standard textbooks make no mention of this method, and the literature concerning it is surprisingly scarce in comparison to the voluminous reports on other methods of analgesia and anesthesia." Waldman does not present any clinical material, but merely discusses the advantages, indications and technique of pudendal nerve block. Urnes and Timmerman⁵ advocate its use routinely in spontaneous breech deliveries. Abrams⁶ used pudendal nerve block in 400 routine deliveries. Some of the advantages of this method stressed by these authors are: (1) It may be used in home practice, when there is a lack of trained assistants to administer inhalation anesthesia and to control the patient when she is unconscious. (2) The patient is awake at all times and is able to cooperate in such procedures as repair of episiotomies. (3) The pelvic floor is relaxed to such a degree that an episiotomy is often not necessary and if so can be performed without additional anesthesia. (4) Eclamptic and preeclamptic patients are especially susceptible to pneumonia, and inhalation anesthesia is contraindicated in such cases. (5) There is no maternal or fetal mortality resulting from this method. (6) The uterine musculature is not involved, so that there is no interruption of uterine contractions during the second stage. This factor also lessens the likelihood of the need for manual removal of the placenta or the occurrence of post-partum hemorrhage. (7) Breech deliveries are facilitated because of the ability to obtain marked relaxation of the pelvic floor, without relaxation of the uterus.

While these advantages are obvious, it is proposed to confine the present paper to the use of pudendal nerve block as the method of choice in cervical dystocia, and discuss some of the theoretical aspects of its

THE EFFECT OF LOCAL ANESTHESIA BY MEANS OF PUDENDAL NERVE BLOCK WITH NOVOCAIN ON CERVICAL DYSTOCIA OCCURRING LATE IN THE FIRST STAGE OF LABOR*

A Preliminary Report

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HUNT and McGee¹ in a recent article state: "One of the most trying dilemmas encountered in obstetric practice is with the patient who, after many hours of active labor, presents urgent indications for delivery but presents an incomplete dilatation of the cervix. Cesarean section usually is not merited because there is no actual bony disproportion, or is contraindicated by frank or potential infection. Manual dilatation of the rigid cervix now is branded as 'manual tearing' and is condemned because of the dangers of trauma and hemorrhage, with morbidity both immediate and remote." With these remarks the majority of practicing obstetricians are in full agreement.

In their article, from which the above paragraph is quoted, they review their findings in the use of Dührssen's incisions in a series of 592 cases and conclude that it offers a rapid surgical method to complete dilatation of the cervix when urgent need for delivery arises, and when the almost fully dilated but resistant cervix is the only obstructing factor. The procedure which they used was first described by Dührssen in 1896. Williams² has remarked concerning this operation: "Unfortunately, it requires some surgical skill on the part of the operator, as well as specially devised specula, and the aid of several competent assistants, so that its use must be limited to trained specialists."

Although Dührssen's incisions constitute a clean surgical procedure, and would be expected to limit the injuries which accompany manual dilatation, it would be more desirable to paralyze the partially dilated spastic cervix by means of the nerve block technique with a local anesthetic such as novocain. If this aim could easily and readily be accomplished, the cervix would become fully dilated, or become so non-resistant that further dilatation could be accomplished by repeated small doses of pituitary extract or by manual means without any danger of

*Valuable assistance in the compilation of this article was rendered by Dr. Ephraim Scharfman.

in the inferior hypogastric plexus. From the latter fibers are distributed peripherally to the pelvic viscera. The afferent or sensory fibers probably pursue a course similar to the efferent or motor nerves. . . . The intermesenteric nerves, before descending over the aorta, also receive peripheral rami from the lumbar sympathetic ganglia."

The pudendal nerve is derived from the second, third, and fourth sacral nerves. It leaves the true pelvis through the greater sciatic foramen and then curves over the spine of the ischium, beneath the gluteal muscles. It enters the anal portion of the perineum through the lesser sciatic foramen, and runs along the lateral fascial wall of the ischiorectal fossa, in the space known as Alcock's canal. The latter is

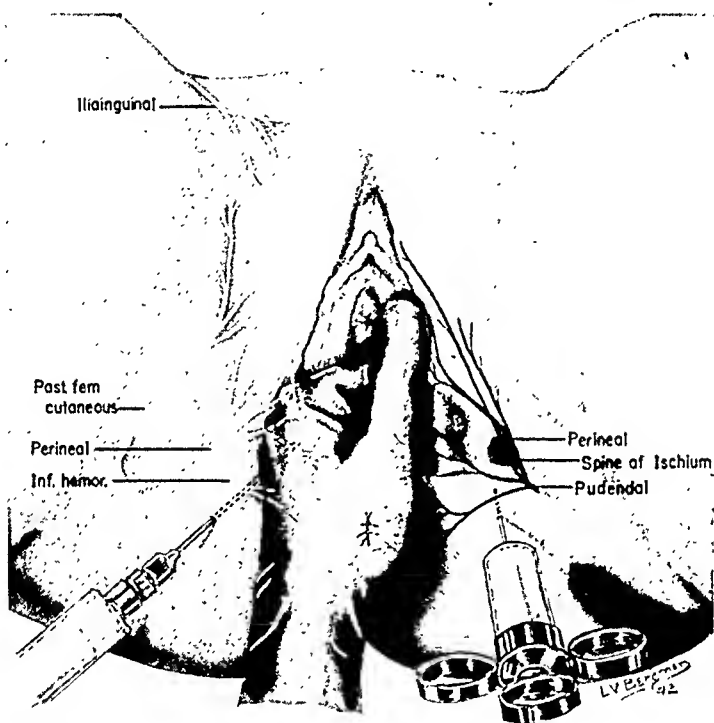


Fig. 2.—Diagram showing the procedure used for blocking the nerve supply to the pelvic floor.

anatomically and surgically important, for it is here that the pudendal nerve is blocked, as will be described further on. In Alcock's canal the pudendal nerve is accompanied by the internal pudic vessels and all together run forward in a groove on the inner border of the tuberosity of the ischium, immediately in front of the attachment of the sacrotuberous ligament.

Other parasympathetic fibers arise from S1, S2, and sometimes from S3 or from S2, S3, and S4 and unite to form the pelvic nerve, which terminates in the inferior hypogastric plexus.

Procedure

With the patient in the lithotomy position, the ordinary technique of preparation is carried out. One-half ounce of Scott's solution may be instilled into the vagina, if an antiseptic solution has not been used

mode of action. Those types of cervical dystocia which result from cephalopelvic disproportion, radium therapy, laceration from previous deliveries, or other conditions which interfere with the normal anatomy of the cervix are to be eliminated from this consideration.

No attempt will be made to give a complete description of the nerve supply to the uterus, because there still exists much controversy on this subject (Fig. 1).

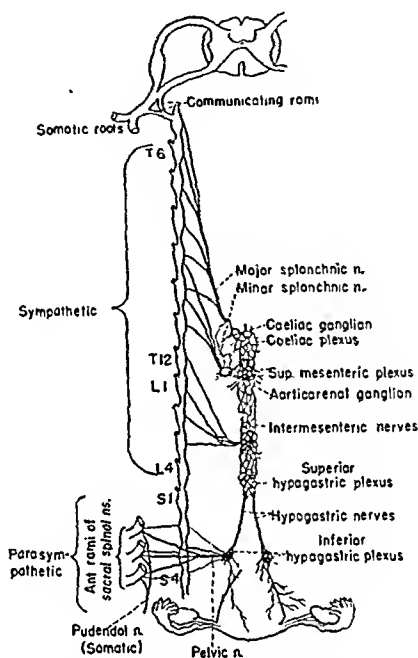


Fig. 1.—Anatomic distribution of the somatic and autonomic nerve fibers of the pelvic viscera. (Modified from Mussey and Wilson, AM. J. OBST. & GYNEC. 42: 760, 1941.)

It is a well-known fact that the sympathetic nervous system supplies most of the nerves to the pelvic organs, and only a few fibers are derived from the parasympathetic system. Recently Labate⁷ published the results of a study on the anatomy of the superior hypogastric plexus, based on 75 dissections. We quote from his article:

“Motor Component of the Superior Hypogastric Plexus.—Two or more parallel nerve bundles are arranged over the anterolateral surface of the aorta, usually one, or perhaps two, on each side. These are known as the intermesenteric nerves. They originate from the inferior pole of the coeliac plexus, at the level of the superior mesenteric artery, and descend over the anterolateral surface of the aorta. Below the point of bifurcation of the abdominal aorta into right and left common iliac arteries the intermesenteric nerves become the main components of a triangular shaped plexus—the so-called superior hypogastric plexus. This plexus descends for a distance of 6 to 8 cm., overlying the lumbar vertebrae in the space between the right and left common iliac arteries. Over the middle of the first sacral vertebra the superior hypogastric plexus divides into the right and left inferior hypogastric nerves. Each of these continues downward to the lateral rectal space, where it ends

This procedure was satisfactory in the majority of our cases. In the case that failed, local anesthesia was likewise unsatisfactory. The explanation for this is that the pudendal nerve was probably not well anesthetized, or that the anesthetic solution was defective. It is essential that the novocain used be always freshly prepared. In neurotic individuals, we suggest a little gas anesthesia during the performance of pudendal block.

This procedure failed in one case. The patient, a para 0 at term, aged 43 years, with an unusually rigid perineum. The membranes had ruptured spontaneously twenty hours prior to admission. After being in the hospital for forty-eight hours, the patient began to have slight irregular contractions following medical induction. Labor continued for twenty-six and one-half hours when the cervix became four fingers dilated and remained at this stage of dilatation for six hours. Local block was tried, and after thirty minutes the cervix still remained spastic and the fetal heart became slightly irregular. Labor was terminated by Dührssen's incision and application of midforceps under general anesthesia. Mother and baby left the delivery room in good condition.

The average duration of labor for the 38 cases was 31.9 hours, and the average arrest of progress lasted 6.3 hours.

In one case there was no arrested progress, but the patient, para i, gravida ii, was admitted to the hospital with membranes ruptured and history of profuse hemorrhage two hours prior to admission. Bleeding had ceased when she came to the hospital because the head had descended and compressed the bleeding site. The fetal heart was slow. Labor pains were rather severe and on rectal examination the cervix was found to be thick and over three fingers dilated. The presenting part was a vertex and was at the level of the spines. Local block anesthesia was considered for two reasons: (1) to allow for rapid dilatation of the cervix without traumatizing it, and (2) to avoid using general anesthesia for fear of relaxing the uterus and causing recurrence of hemorrhage. Fetal distress necessitated rapid delivery. Within ten minutes after the local anesthesia, the cervix became completely dilated, and labor was terminated with low forceps, resulting in the delivery of a live baby in good condition.

In the majority of cases it was necessary to use pituitary extract in two or three minim doses because a state of moderate secondary inertia existed. Although some obstetricians would have tried pituitary extract without this method of block anesthesia, it has been observed by the authors that such use of oxytocics often fails to accomplish the desired results.

In this series, maternal exhaustion with a spastic resistant rim of cervix remaining at a standstill, for an average of 6.3 hours, was found to be the most frequent indication for intervention. Most cases required outlet forceps to complete delivery. Labor was terminated in every case after the use of local block anesthesia, and the average length of time from injection to the birth of the child was 21½ minutes.

An episiotomy was done in every case and all healed by primary union with the exception of two. In these cases the sutures sloughed the third day, although the temperatures in both cases remained normal. The patients offered the ordinary complaints during the puerperium.

Two patients sustained cervical lacerations which were repaired after the expulsion of the placentas. These were examined on the day of discharge and found healed by primary union.

previously. The index and middle fingers of one hand are inserted in the vagina and the ischial spine is located and used as an anatomic landmark. A No. 19 needle attached to a 20 c.c. syringe is inserted medially, half way between the rectum and tuberosity of the ischium. When the needle is felt by the vaginal fingers it is directed downward and laterally to a point just below the ischial spine. This directs the needle into Alcock's canal. Then 20 c.c. of 1 per cent novocain is injected at this point. One must always remember to pull back the plunger before injecting the solution, for, as pointed out above, the pudendal nerve is accompanied by the internal pudic vessels in its course through Alcock's canal. The needle is left in situ and the syringe is disconnected, refilled with 15 c.c. of the solution of 1 per cent novocain, and reattached to the needle. The latter is withdrawn slightly and directed against the ischial tuberosity, where the anesthetic is injected around the lateral cutaneous femoral nerve. Then 15 c.c. of 1 per cent novocain is injected superficially in an oblique and radial manner from the original site of insertion of the needle, to the inner aspect of the labium majus, thus paralyzing the terminal branches of the ilioinguinal nerve. A similar procedure is carried out on the opposite side. Thus, a total of 100 c.c. of novocain is used for both sides. As seen from the above, the needle has to be inserted only in two places, one on the right and one on the left side, without the need for removing it entirely during each procedure (Fig. 2).

Indications .

A. Maternal.—1. In severe exhaustion in spite of treatment, when progress has been arrested in the course of a prolonged labor apparently due to the resistance of a rigid rim of cervix.

2. In serious pre-eclampsia or eclampsia when rapid dilatation of a rigid cervical rim may become desirable.

3. In cardiac decompensation during labor, when the rapid elimination of a rigid cervical rim is of importance before delivery can be accomplished safely.

4. In any emergency, such as abruptio placenta with concealed or external bleeding, when labor is well advanced but a cervical rim still exists.

B. Fetal.—1. Prolapsed cord in the presence of a resistant cervical rim.

2. Marked or progressive irregularities of fetal heart sounds, or passage of meconium under the same circumstances.

Results in 38 Cases

Thirty-eight patients were treated for cervical dystocia late in the first stage of labor by the technique described above. Thirty-one of the patients were primiparas and 7 were multiparas. There were no maternal deaths among the 38 cases.

There was one stillbirth, due to intracranial injury following the application of forceps, in a case of cephalopelvic disproportion.

Generally about five to ten minutes after the anesthetic is injected, one notices a relaxation of the perineum. In another ten minutes the spasticity of the cervix disappears and dilatations progress satisfactorily if the uterine contractions continue. If there is uterine inertia, small repeated doses of pituitary extract (2 min.) will initiate further progress.

THE ASSOCIATION OF VAGINAL BLEEDING TO ORGANIC PATHOLOGY AND THE ENDOMETRIAL PATTERN IN THE DECADES BEFORE THE MENOPAUSE

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THE commonest complaint of women presenting themselves to the physician is abnormal vaginal bleeding. In many instances the simplest examination seems to disclose the cause, in others careful diagnostic procedures are required, while in a considerable group the factors producing the bleeding are not known.

Material

A study of all patients in whom abnormal bleeding was a symptom, admitted to the Gynecological Service of Roosevelt Hospital from 1921 to 1935, provided the material for this presentation. During these years 12,350 patients were admitted to the wards. Abnormal bleeding in some form was noted in 4,362 patients, or 35.3 per cent, of whom 15.6 per cent gave no evidence of pregnancy. This may be compared with the report of Weintraub¹ who found that 16.6 per cent of 4,421 patients admitted to the gynecologic service of the Israel Zion Hospital (Brooklyn), presented with abnormal bleeding not due to pregnancy.

Of our entire series, 406 were classified as postmenopausal. They were over forty years of age and had experienced six months' amenorrhea before the bleeding occurred. These cases were analyzed in a previous paper by Taylor and Millen.²

The present study deals with 3,956 cases in women before the menopause. The age distribution is shown in Table I. This compares with the figures of Keene and Payne³ who, in a series of 500 patients with functional bleeding, noted that 4 per cent occurred before twenty years; 21 per cent occurred between twenty and thirty; 25 per cent between thirty and forty; 41 per cent between forty and fifty; and 9 per cent between fifty and sixty years of age. Their inclusion of postmenopausal cases created a higher percentage in the last two decades.

The intent had been to study and reclassify all the microscopic slides of each case. Records from the earlier years frequently lacked the

TABLE I. AGE DISTRIBUTION OF CASES BEFORE MENOPAUSE

AGE BY DECADES	10-19	20-29	30-39	40-49	50	TOTAL
Cases with good endometrial slides available for restudy	10	216	181	409	69	885
Cases with no endometrial slides available	93	963	1,210	713	92	3,071
Total	103 (2.5%)	1,179 (29.8%)	1,391 (35.1%)	1,122 (28.3%)	161 (4.3%)	3,956

The average duration of ruptured membranes in the 38 cases was 11.9 hours.

Clinical Discussion

No attempt will be made to explain, from an anatomic or physiologic basis, the clinical results obtained in the type of cases in which this procedure was used. For, as pointed out above, there still exists much controversy as to the exact pathways of the nerve supply to the uterus. The hypothesis is advanced that reflex stimuli may be set up, as the result of local anesthesia of the pudendal nerve, which in some way affect uterine activity, particularly in relation to the cervix. The problem of the reflex activation of the uterus has been investigated on numerous occasions. As pointed out by Kuntz,^s “. . . the data available at present speak against the existence of reflex connections in the autonomic ganglia (except in the peripheral plexuses), but physiological data is not wanting which strongly suggest that under certain conditions reflex reactions may be carried out through these ganglia. Sokownin (1874) observed that after all the nervous connections of the inferior mesenteric ganglia except the hypogastric nerves were out, stimulation of the central end of one hypogastric nerve elicited contraction of the bladder, the efferent impulses passing down the hypogastric nerve on the opposite side. Langley and Anderson (1894) confirmed this finding. They also observed that stimulation of the central end of one hypogastric nerve, under the same experimental conditions, also elicits slight pallor of the opposite cornu of the uterus, and rarely, slight contraction of this part of the uterus and the vagina.

“Stimulation of the mammary gland elicits uterine contractions which may give rise to painful sensations. Uterine contractions in response to stimulation of the breasts become more pronounced near the termination of pregnancy. Reflex reactions of the female genitalia also may be elicited by direct stimulation of any afferent nerve.”

In view of the fact that favorable results have been attained with this procedure, even without an adequate neuroanatomic explanation of its mechanism, it is believed to be of sufficient interest and value to present to the medical profession for further consideration.

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innocent lesions, such as cervical erosion and vaginitis. The specific infections may cause bleeding by a local reaction in the endometrium or through an interference with the ovarian mechanism and a resulting dysfunction.

Erosions of the cervix undoubtedly are as capable of producing bleeding from the local lesions as any abrasive type of wound would do. An erosion of the cervix, however, may exist in a patient suffering from abnormal functional bleeding.

Malpositions such as retroversion and prolapse, do not cause bleeding unless there is a sufficient engorgement produced in the uterus through its position, which restrains blood return, or unless there is an associated functional effect on the endometrium.

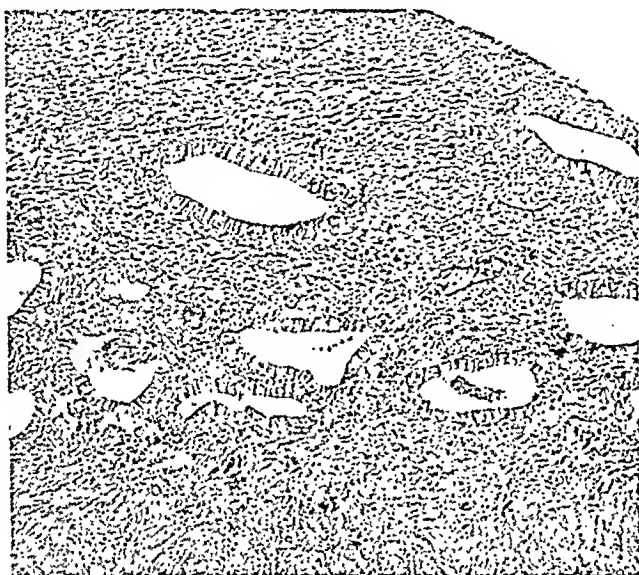


Fig. 1.—Flattened endometrium in state of hyperplasia overlying a fibroid (SC 2668). Patient had had menorrhagia for ten months; 21 days since last menstruation.

Blood dyscrasias are infrequently found associated with vaginal bleeding and might be considered as an organic cause. Kahn¹⁵ reported 42 cases of blood dyscrasias of all types with 51.1 per cent having normal menstruation, 33.3 per cent having excessive and 15.5 per cent having diminished menstruation.

The Endometrial Patterns in Relation to Bleeding.—Abnormal bleeding may occur in patients with grossly normal pelvic organs with the endometrial pattern of a normal cyclical phase. Many terms are used to designate the phases of the normal cycle, but we have used the simple classification of early follicular phase, follicular phase, early corpus luteum phase, and premenstrual phase. Although the time of the cycle is usually easily recognizable, Evans and Swezy¹⁶ maintain that premenstrual changes may occur immediately following menstruation and point out the hazards of comparing specimens, but Novak¹⁷ feels that in the small percentage of cases of bleeding from secretory epithelium, the musculature may be at fault, or a vasomotor disorder affecting the vascular system may cause bleeding. Traut and Kuder¹⁸ believe that an alteration of the corpus luteum phase may occur as a result of a weak but prolonged effect of the corpus luteum. As a result of their

dates of the menstrual period before operation and endometrial section slides were often missing or inadequate to determine endometrial patterns. Hence the cases have been subdivided according to the value of the material for study as shown in Table I.

Classification of Causes of Bleeding

Classifications of the causes of abnormal vaginal bleeding usually make a basic subdivision between functional types without gross pathology on the one hand and organic lesions on the other. The latter include complications of pregnancy, malignant and benign tumors, inflammatory reactions and malpositions. There are also a few constitutional causes such as certain of the blood dyscrasias and perhaps vitamin deficiencies.

Complications of pregnancy are an important cause of abnormal vaginal bleeding, but this is a subject for special consideration elsewhere. It may be noted, however, that in this series out of 3,956 cases of vaginal bleeding in women before the menopause, 861, or 21.8 per cent, were due to miscarriage, ectopic pregnancy, or hydatidiform mole. Rongy⁴ found 1,167 such complications among 2,175 patients admitted to the gynecologic service at the Lebanon Hospital, New York City.

Cancer as a cause of bleeding is only of statistical interest, for the mechanism of the hemorrhage is quite obvious. In this series, malignant tumors numbered 611, or 15.4 per cent. Ovarian cancer must be considered from a somewhat separate viewpoint because here the bleeding is likely to come from an endometrial reaction to hormones produced by the tumor tissue. Shaw,^{5, 6} Meyer,⁷ and, more recently, Seegar and Jones⁸ have described such cases. A similar relationship between vaginal bleeding and benign ovarian tumors may also exist.

The *benign tumors* which may cause bleeding are chiefly fibromyomas, benign ovarian tumors, and polyps. Fibroids are, of course, the most important and the manner in which they cause bleeding is of interest. As pointed out by Burch,⁹ the bleeding in fibromyoma is due in some instances to a functional disturbance manifested in a peculiarity of the endometrial pattern and not to the fibromyoma itself. Morse¹⁰ claims that myomas produce menorrhagia until they undergo necrotic changes when metrorrhagia ensues. Jones¹¹ emphasizes that bleeding occurs when a fibroid projects into the cavity, and Burch⁹ also believes that erosion of the tumor through interference with the blood supply may lead to bleeding. The excess endometrium overlying a fibroid has also been suggested as a cause of the bleeding (Faber¹²).

The relationship of the ovarian hormones to fibroids has received considerable attention. Witherspoon¹³ believes that fibroids and hyperplasia of the endometrium associated with follicular cysts are the result of the hormonal activity of the cysts. As reported by Twombly and Millen,¹⁴ pellets of estrogenic hormone inserted to produce a prolonged therapeutic effect in the menopause are capable of rapidly increasing the size of existing fibroids and producing hyperplasia of the endometrium through their prolonged effect.

The cause of bleeding in polyps needs little discussion. They are often multiple, frequently missed and not infrequently associated with myomas.

The term *inflammatory* usually includes the specific pelvic infections, gonorrhea, tuberculosis, and post-partum infections, as well as the more

A condition of hypertrophy without hyperplasia exists when certain hormonal imbalances produce a decidual-like hypertrophy of the stroma cells without any glandular increase. Reinhardt²³ described a case in which this progressed to a marked degree.

Adenomyosis may exist with the endometrial patterns in all the normal cycles as well as hyperplasia and atrophy. Not infrequently the islands do not react as does the rest of the endometrium.

As described by Kotz and Parker,²⁴ Graves,²⁵ Traut and Kuder,¹⁸ Hamblen,²⁶ and Jones,²⁷ mixed endometrial patterns may contain secretory glands in a follicular stroma, or follicular glands in a secretory stroma, as well as both types of glands existing together. Fig. 3 shows a nonreacting cystic gland in corpus luteum phase endometrium.



Fig. 3.—Nonreactive cystic glands in typical secretory endometrium (SC 141). Patient, aged 45 years, had a fibroid and metrorrhagia for two months.

Although *chronic endometritis* does not entertain the popularity as a diagnosis that it did a decade ago, there is little doubt of the frequency of this endometrial pattern. The inflammation may be chronic with the characteristic round cell infiltration in any phase of the endometrial cycle, or actually an acute inflammatory process may exist.

Results

The cases of this series have been carefully reviewed and the most apparent cause for bleeding assigned to each. These are shown in Table II.

Complications of pregnancy occurred in 861 cases, or 21.8 per cent of the total, divided into age groups.

External cancer was a cause of bleeding in 611, or 15.4 per cent, of the 3,956 cases divided in age groups. Carcinoma of the ovary occurred in ten instances and in all age groups below fifty, but no endometrial slides were available to determine the cause of the bleeding.

studies of blood estrin, prolan titer, and the histology of the endometrium in a series of 97 cases, they decided that bleeding might be due to a mal-decidualation of the endometrium as a result of prolonged and exhausting secretory activity in the glandular elements and associated stromal changes. Anspach and Hoffman¹⁹ found a large percentage of cases in each age group in bleeding from normal endometrium.

The term, *atrophic endometrium*, needs clarification. There certainly is a definite type of endometrial pattern associated with a hormonal decrease resulting from castration or aging, which can be considered an atrophic condition with decreased glandular elements in a thin endometrium. Novak¹⁷ has described instances after the menopause where



Fig. 2.—Atrophy and fibrosis (SB 8876).

cystic changes occur in this atrophic endometrium, indicating a hormonal imbalance as well as diminution. There is also, however, a mechanical type of "atrophy" found over a fibroid which is really a thinned or flattened endometrium. This may show any one of the normal cyclical changes on an abnormal form as hyperplasia (Fig. 1). A third type of atrophy may occur from a purely local uterine condition of endarteritis as seen in fibrosis uteri (Fig. 2).

The term *hyperplasia*, for which Novak popularized the phrase, "swiss cheese endometrium," has been too frequently described to need elaboration. Herrell²¹ prefers the term cystic endometrium, feeling that the cystic formation is a result of an ovarian failure as it occurs in all phases of the endometrium. Randall and Herrell²² found abnormal bleeding to occur in cystic endometrium associated with corpus luteum phase. However, it was noted only in the early corpus luteum phase. In their series cystic endometrium in late corpus luteum phase was not associated with abnormal bleeding. Most writers feel, however, it is produced by a prolonged and unopposed production of estrogenic hormone.

TABLE IV. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH SUBMUCOUS FIBROIDS

AGE BY DECADES	20-29	30-39	40-44	45-49	50
<i>Normal Endometrium</i>					
Premenstrual	0	0	8	7	3
Early corpus luteum	0	2	0	0	0
Late follicular phase	0	1	11	8	5
Early follicular phase	0	0	2	0	0
<i>Hormonal Changes</i>					
Hypertrophy without hyperplasia	1	0	0	0	0
Hyperplasia	0	0	4	7	1
Atrophy	0	0	4	3	1
Mixed endometrium	0	0	0	1	0
<i>Flattened Endometrium</i>					
Corpus luteum phase	0	2	1	0	0
Late follicular phase	0	0	0	0	2
Early follicular phase	0	0	0	0	1
<i>Adenomyosis</i>					
Corpus luteum phase	0	2	2	1	0
Late follicular phase	0	0	1	1	0
Hyperplasia	0	0	1	0	0
Atrophy	0	0	1	2	0
<i>Inflammations</i>					
Chronic endometritis	0	1	1	0	1

Adenomyosis was found in association with fibroids in only 14 cases, but this undoubtedly represents a smaller figure than is actually the case, since numerous sections are necessary to exclude this possibility. Hyperplasia was noted in one case and atrophic endometrium in another. The remaining cases showed normal endometrial patterns in the different phases of the cycle.

Fibroids were found associated with polyps in 36 instances, these being distributed through all age groups but with the highest incidence between forty-five and forty-nine years of age. Only 17 of these cases had endometrial slides available for study, and of these 7 showed only the polypoid structure. The others were diagnosed as normal endometrium except for one case of flattened endometrium in early follicular phase and two cases of chronic endometritis.

We did not find evidence to support the view of Witherspoon¹³ that the small follicular cysts were an integral part of the pathogenesis of myomas as they were absent in many instances and are, of course, known to be present in many cases not associated with fibroids. Therefore, we only included ovarian tumors over 3 cm. in diameter among the cases labeled as fibroids with ovarian tumor. Thirty such cases were noted with their principal number between 30 and 39 years of age. Ovarian tumors associated with fibroids were of the following types: dermoids, 5; corpus luteum cysts, 3; and retention, follicular, or serous cysts, 22. In only 8 cases were endometrial specimens available. Two dermoids were associated with late follicular phase, one corpus luteum cyst was associated with corpus luteum phase and the other endometrial patterns, associated with serous or follicular cysts, were early follicular phase, one; late follicular phase, two cases; atrophy, one case; and chronic endometritis, one case.

Fifty-two benign ovarian tumors were found, these being distributed in all age groups with the principal age incidence from twenty to twenty-nine. Again 3 cm. was taken as an index of cyst size to

TABLE II. ANALYSIS OF THE CAUSES OF BLEEDING IN 3,956 CASES

AGE BY DECADES	10-19	20-29	30-39	40-49	50
<i>Pregnancy</i>	38	472	306	45	0
<i>Cancer</i>					
Of uterus and vagina	9	29	268	271	34
Of ovary	1	2	3	4	0
<i>Benign Tumors</i>					
Fibroids, intramural and subserous	0	51	314	340	61
Submucous fibroids	0	1	14	136	21
Fibroids and adenomyosis	1	0	13	0	0
Fibroids and ovarian tumors	0	0	25	3	2
Fibroids and polyps	1	2	6	21	6
Ovarian tumors	1	15	15	19	2
Endometrial polyps	0	4	6	12	3
Cervical polyps	1	5	15	17	1
Urethral polyps	0	3	0	0	0
Endometriosis alone	0	0	2	0	0
<i>Inflammations</i>					
Pelvic infections	34	367	205	53	4
Cervical erosions	7	100	70	33	5
Senile vaginitis	0	0	0	0	2
<i>Malposition</i>	2	44	22	5	0
<i>Grossly Normal</i>	8	84	107	163	20

TABLE III. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH FIBROIDS (INTRAMURAL AND SUBSEROUS)

AGE BY DECADES	20-29	30-39	40-44	45-49	50
<i>Normal Endometrium</i>					
Premenstrual	2	8	31	9	4
Early corpus luteum	5	25	0	0	0
Late follicular phase	13	14	24	20	13
Early follicular phase	2	5	3	4	0
<i>Hormonal Changes</i>					
Hypertrophy without hyperplasia	2	0	1	0	0
Hyperplasia	3	8	12	10	3
Atrophy	0	1	4	3	6
Mixed endometrium	0	5	0	0	0
<i>Flattened Endometrium</i>					
Corpus luteum phase	0	1	1	0	0
Late follicular phase	1	2	0	0	2
Hyperplasia	0	1	0	0	0
Atrophy	0	0	0	0	1
<i>Adenomyosis</i>					
Corpus luteum phase	0	0	4	0	0
Late follicular phase	0	0	4	4	1
Hyperplasia	0	0	0	2	1
<i>Inflammations</i>					
Acute endometritis	0	1	1	0	0
Chronic endometritis	3	5	2	2	1

Fibroid tumors were found in 938 cases, of which 172 were submucous in location. Slides of the endometrium were available in 369 cases and these are the basis for Tables III and IV which show the different types of endometrial patterns for submucous and other fibroids. The 40 to 49 age group is divided because of the importance of this decade.

This figure is undoubtedly misleading. The patient in whom endometriosis alone is a cause of bleeding is rarely operated upon, as it is frequently difficult to make such a preoperative diagnosis. Perhaps, had every one of the cases listed as grossly normal, or the mild chronic inflammatory cases been subjected to laparotomy, the primary diagnosis of endometriosis would have been much higher.

There were 663 cases of bleeding associated with pelvic organs as the seat of inflammatory lesions due to an infectious process with the highest incidence between 20 and 29 years. Of these, 108 had available slides and 38 of these showed an endometrial pattern of chronic endometritis. Table VII shows the endometrial patterns.

Among 215 cases of cervical erosions, enough histories revealed menorrhagia to cause some speculation as to the cause of bleeding being in the endometrial pattern rather than in the obvious organic lesion. The highest incidence in this group occurred between 20 and 29 years of age with a close second in the 30 to 39 age group. Only 95 had microscopic slides available for study. The endometrial patterns are shown in Table VI.

TABLE VII. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH CERVICAL EROSION

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
<i>Normal Endometrium</i>						
Premenstrual	0	4	2	4	1	0
Early corpus luteum	0	8	3	0	2	0
Late follicular phase	0	17	6	8	4	0
Early follicular phase	0	5	0	0	0	0
<i>Hormonal Changes</i>						
Hypertrophy without hyperplasia	0	5	0	0	0	0
Hyperplasia	0	4	5	3	2	1
Atrophy	0	0	0	1	0	0
<i>Adenomyosis</i>						
Corpus luteum phase	0	1	0	0	0	0
<i>Inflammation</i>						
Chronic endometritis	1	5	1	2	0	0

TABLE VIII. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH GROSSLY NORMAL PELVIC ORGANS

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
<i>Normal Endometrium</i>						
Premenstrual	0	8	1	18	16	2
Early corpus luteum	1	2	3	1	0	0
Late follicular phase	4	12	8	12	7	4
Early follicular phase	0	8	2	1	1	0
<i>Hormonal Changes</i>						
Hypertrophy without hyperplasia	0	10	0	0	0	0
Hyperplasia	0	5	5	16	8	0
Atrophy	0	0	0	0	5	2
Mixed endometrium	1	0	1	0	0	0
<i>Adenomyosis</i>						
Late follicular phase	0	0	0	0	0	1
Early follicular phase	0	0	0	1	0	0
<i>Inflammation</i>						
Chronic endometritis	0	1	2	0	3	1

eliminate the tiny follicular or retention cysts so common in cases without bleeding. The 19 cases with available endometrial and ovarian slides are classified in Table V.

TABLE V. BENIGN OVARIAN TUMORS AND ASSOCIATED ENDOMETRIAL HISTOLOGY

TYPE OF BLEEDING	AGE	PATH. NO.	OVARY	ENDOMETRIAL HISTOLOGY
Both	15	SB 8700	Simple cyst	Chronic endometritis
Metrorrhagia	25	SC 4827	Simple cyst	Follicular phase
Both	24	SC 3459	Simple cyst	Corpus luteum phase
Both	25	SC 3639	Simple cyst	Follicular phase
Metrorrhagia	27	SC 5179	Follicular cyst	Hypertrophy
Menorrhagia	26	SD 144	Simple cyst	Follicular phase
Both	24	SB 9466	Follicular cyst	Hypertrophy
Metrorrhagia	22	SD 2720	Corpus luteum cyst	Adenomyosis
				Follicular phase
Both	24	SC 2458	Corpus luteum cyst (right) Serous cyst (left)	Chronic endometritis
Metrorrhagia	24	SC 7146	Follicular cyst	Chronic endometritis
Both	26	SC 4332	Serous cyst	Hypertrophy without hyperplasia
Both	25	SC 8126	Serous cyst	Hypertrophy without hyperplasia
Menorrhagia	36	SC 797	Dermoid	Chronic endometritis
Menorrhagia	32	SC 1516	Hemorragic cyst	Corpus luteum phase
Menorrhagia	42	SC 3681	Serous cyst	Atrophic
Both	41	SB 2782	Corpus luteum cyst	Follicular phase
Metrorrhagia	44	SC 4303	Indefinite cyst type	Hypertrophy
Metrorrhagia	40	SC 5668	Indefinite cyst type	Follicular phase
				Hypertrophy
Menorrhagia	53	SD 2262	Serous cyst	Atrophic

Twenty-five endometrial and 39 cervical polyps were found, the cervical cases occurring in all age groups, while no endometrial polyps were found in the ten to nineteen age group.

No outstanding endometrial pattern was noted in either group among the cases with available slides.

In a sufficient number of these cases, histories were accurate enough to realize menorrhagia was not an infrequent type of bleeding.

Only two cases of endometriosis alone were found in our series and the patients were at 30 to 39 years and without endometrial studies.

TABLE VI. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH PELVIC INFLAMMATORY DISEASE

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
<i>Normal Endometrium</i>						
Premenstrual	0	2	1	4	1	0
Early corpus luteum	1	2	7	4	0	0
Late follicular phase	0	6	10	0	0	0
Early follicular phase	0	7	3	0	0	0
<i>Hormonal Changes</i>						
Hypertrophy without hyperplasia	0	9	0	0	0	0
Hyperplasia	0	1	2	2	0	0
Mixed endometrium	0	1	0	0	0	1
<i>Adenomyosis</i>						
Late follicular phase	0	0	0	1	0	0
Early follicular phase	0	0	0	1	3	0
Hyperplasia	0	0	0	0	1	0
<i>Inflammations</i>						
Chronic endometritis	1	23	3	11	0	0

THE ASSOCIATION OF MILD EXTERNAL HYDROCEPHALUS WITH DEATH IN THE EARLY DAYS OF LIFE

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AN INCREASE in the amount of cerebrospinal fluid present within the intermeningeal spaces surrounding the brain which is associated with progressive, fatal respiratory distress in the newborn infant has not been previously recognized. We have been aware for some time that there is a small group of infants, usually delivered by cesarean section, who, although normal at birth, subsequently develop respiratory disturbances and fail to survive more than twelve or eighteen hours after birth. These infants almost invariably show a marked increase in intracranial fluid. We were originally of the belief that this increase in fluid occurred only following delivery by cesarean section, and although there is a high degree of correlation between the incidence of external hydrocephalus and cesarean section, we have recently observed similar clinical and pathologic findings when delivery has been by the vaginal route.

External hydrocephalus, the term generally used to indicate an increase in fluid around the brain, is infrequently observed and is in general a poorly defined entity. When present from birth it has been considered as possibly due to (1) intrauterine meningitis, either inflammatory or noninflammatory; (2) nonfunctioning of the mechanism controlling absorption of spinal fluid; (3) stasis caused by pressure on the blood and lymphatic channels of the neck; (4) hypoplasia of the cerebral hemispheres with a resulting compensatory fluid outflow. Shannon¹ believes that an increase in fluid around the brain may result from calcium deficiency and may be the immediate cause of the hyperirritability demonstrated by such patients.

External hydrocephalus has been described in the adult under the term serous or aseptic meningitis. It is essentially an edema of the leptomeninges in which the subpial and subarachnoid spaces are distended with fluid and the true criteria of inflammation are lacking. It has been observed following head trauma, infectious diseases, various intoxications, alcoholism, uremia, and intracranial tumors.

In the infant at birth the amount of fluid within the skull varies with the gestational age. We have reported measurements of this fluid in a previous publication,² and have found that with a birth weight exceeding 2,000 Gm. very little fluid can be demonstrated at autopsy in the majority of infants who die in the first few days of life.

There were 73 patients with pronounced uterine malposition noted with the highest incidence between 20 and 29 years of age. Although only 33 cases had available endometrium these were enough to point out that no endometrial pattern is typical. All of the normal phases as well as the hormonal influence as portrayed by hyperplasia, and hypertrophy without hyperplasia, and the mixed endometrium were present. Chronic endometritis was noted in one instance.

Grossly normal pelvic organs were noted in 382 cases with slides available in 173 cases, as shown in Table VIII.

Discussion

From the above results we would like to offer the opinion that abnormal vaginal bleeding is not caused by any one organic pathologic condition or endometrial pattern, but rather it is a symptom frequently associated with one of these lesions and a principal one in bringing the patient to present herself for advice. Patients with these same lesions often present themselves with other symptoms than bleeding, just as a third group, having no symptoms, is never examined and the lesion is found at autopsy, or as a physical finding when examined for some other disease.

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all, and, in addition, minimal early pneumonia in four instances, petechiae of the thoracic viscera in 2 and a small intraventricular clot within one cerebral hemisphere in 1. The amount of fluid within the head was measured in 7 cases. It varied from 15 to 73 c.c. with an average of 38.7 c.c.

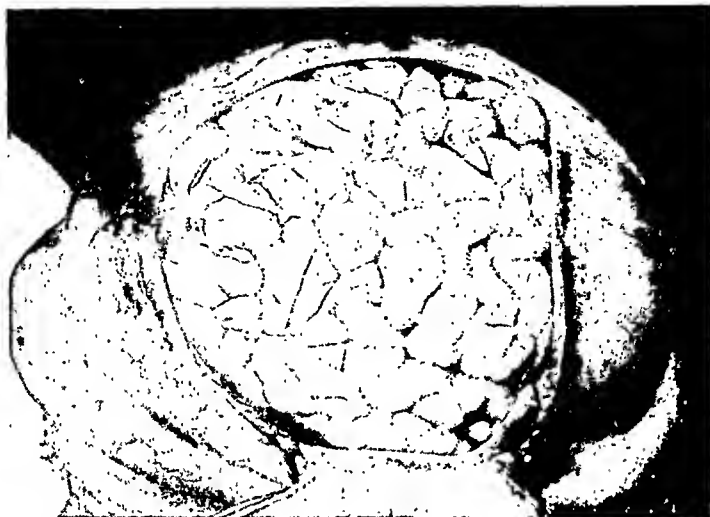


Fig. 1.—Skull opened by the Bencke technique showing normal convolutions and no visible fluid. Aged 13 hours, weight 2,600 Gm. Spontaneous cephalic delivery.



Fig. 2.—Skull opened by the Bencke technique showing marked increase in intracranial fluid. Forty-five cubic centimeters were measured. Aged 8 hours, weight 2,345 Gm. Cesarean section because of inadequate pelvic size.

The indications for the cesarean sections had been placenta previa 3, cephalopelvic disproportion or contracted pelvis 5, partial premature detachment of the placenta 1, rheumatic heart disease 1, elective section with sterilization 1, and incomplete rupture of the uterus one. The membranes were intact at the time of cesarean section in 10, with no record being available in the other 2. Three patients had had mild labor pains for three, four, and eight hours, respectively. The type of anesthesia included cyclopropane 5, ethylene 3, novocain 2, and unrecorded 2.

In the infants to be described in this report a marked increase in the amount of intracranial fluid has been found within each skull, the measurable volumes ranging from 15 to 74 c.c. The meningeal vessels in such cases are raised from the surface of the brain and appear to float in fluid. After the cranial cavity is opened this fluid drains quickly from the brain surface and meninges and is consequently visible only in the freshly opened skull. Free fluid is usually observed in the cranial fossae after the brain has been removed.

The clinical histories of these infants are remarkably similar. Practically all breathe immediately after birth, and they are sent to the nursery as normal newborn infants. Within a short time, varying from a few minutes to a few hours, they develop respiratory distress which becomes progressively worse despite all therapeutic measures. Such infants usually breathe irregularly and with apparent difficulty, often with marked costal retraction. Cyanosis develops and frequently there is evidence of cerebral irritation in the form of a weak high-pitched cry, restlessness, muscle spasm, or even convulsions. A clinical diagnosis of atelectasis, pneumonia, congenital heart disease, or intracranial hemorrhage is usually made. At autopsy, however, it is rare to find definite pathologic lesions which are sufficient to explain satisfactorily the cause of death. Varying degrees of atelectasis are usually present but the alveolar nonexpansion is almost never primary in character, and instead is a result of the gradual resorption of air which takes place during the agonal period. The one pathologic condition which has been demonstrated in all of these infants is an amount of cerebrospinal fluid greater than that ordinarily seen.

Material

From our own hospital and from other institutions in the city we have observed 20 infants weighing over 2,000 Gm. who have had excessive amounts of fluid within the skull and who have shown a clinical course similar to that described above. Twelve were delivered by cesarean section; 8 were vaginal deliveries, 4 of which followed late artificial rupture of the membranes (breech 2, low forceps 2) and 4 of which followed spontaneous rupture of the membranes (natural cephalic 3, low forceps 1).

The infants delivered by cesarean section lived from five to thirty-five hours. Respiration was established promptly in 6 and in the other 6 was delayed, irregular, or shallow for five to ten minutes after birth, and in one instance remained so for one and one-half hours. All but one were considered normal infants on admission to the nursery. Following the establishment of normal respiration all twelve infants later developed respiratory distress. The symptoms prompted a clinical diagnosis of intracranial hemorrhage twice, congenital heart disease once, and congenital atelectasis in most of the remainder. Oxygen administration, drug stimulation, tracheal aspiration, and artificial respiration were of no avail. Autopsy revealed excessive intracranial fluid in

followed by extravasation of fluid into organs and body cavities and that an accompanying subarachnoid accumulation of cerebrospinal fluid may be produced.

In support of this belief are the findings of Nicholson,⁴ who has shown that dogs subjected to low alveolar oxygen concentrations for short periods of time exhibit a decrease in the flow of cerebrospinal fluid while exposure over longer periods tends to increase the flow. High carbon-dioxide concentrations also tend to increase the flow of fluid.

The clinical course and pathologic findings in the infants reported by Clifford are similar to those that we have described above. It is interesting to note that all were delivered by cesarean section in association with placenta previa, while in our series only three of the infants delivered by the same method were subjected to this procedure because of placenta previa. We have observed a large number of infants delivered through the vagina who have died following placenta previa and premature detachment of the placenta where death was definitely due to anoxia. Although there is often a slight extravasation of fluid and red blood cells into the meningeal spaces in such cases, the amount of fluid is rarely as great as that found following delivery by cesarean section. Our experience suggests that the method of delivery may be more important in the production of increased fluid than is the indication for the operation.

Why only certain infants should exhibit this increase in meningeal fluid is not clear. It occurs proportionately much more often in association with birth by cesarean section for these infants represent only about one-twentieth or less of all those born. In general infants delivered by this method vary from those born by the vaginal route only inasmuch as they are suddenly removed from the intrauterine environment, instead of being subjected to the pressure exerted by uterine contractions and the passage of the head through the birth canal. One could conceive that a greater amount of fluid than we ordinarily realize is present within the cranial vault during intrauterine life; that nature has provided it for protection during birth in order that molding of the skull may not cause damage to the brain substance; that normally it is reduced in amount during the process of birth, and that when the head does not pass through the pelvis, the amount normal to intrauterine life remains. On the other hand it could also be possible that relatively little fluid is present while the infant is within the uterus, but that when suddenly removed, the reduction in pressure to which it is subjected, causes an extravasation of fluid into the spaces around the brain.

The group which is particularly affected is made up of those infants who are slightly premature and have a birth weight between 2,000 and 2,500 Gm. Of the 25 infants discussed in this report, 16 weighed from 2,000 to 2,500 Gm., 6 from 2,500 to 3,000, and only 3 were over 3,000 Gm.

Of the 4 infants delivered following late artificial rupture of the membranes by methods other than cesarean section, two breathed spontaneously immediately after birth and appeared entirely normal. Respiration was delayed two minutes and a tracheal catheter was used in the third, and in the fourth respiration was never normally established. The last infant lived only one hour. The first three survived eighteen, forty-five, and fifty hours and the clinical course of each was similar to those dying after cesarean section. At autopsy there was slight interstitial pulmonary hemorrhage in 2 and no abnormality exclusive of increased fluid in the other 2. The amount of fluid within the head was 22, 30, 32, and 55 c.c. Labor lasted from four hours to seven and one-half hours. No significant maternal complications were present.

The 4 remaining infants were delivered after spontaneous rupture of membranes. Respiration was promptly established in 3, although it remained irregular or shallow for some time in 2 of these. In the fourth, respiration was slightly delayed but soon became normal. These infants lived three, twelve, thirteen, and eighteen hours and showed a repetition of the clinical findings noted in the previously described infants. Labor was less than six hours in 3, and thirty-three hours in the fourth. No maternal complications were present. At autopsy early pneumonia was found in one and petechiae of the thoracic viscera in 2. Fluid measurements were 22, 25, 40, and 74 c.c.

In addition to the 20 infants born alive, 5 others have been found who exhibited a marked increase in intracranial fluid. These died in the intra-partum period shortly before birth. One of these was delivered by laparotomy following rupture of the uterus which had resulted in extrusion of the infant into the abdominal cavity. The other 4 were delivered vaginally without instruments following artificial rupture of the membranes. Two of the infants were known to have been alive at the time of membrane rupture and the other two were alive at the last examination for heart tone prior to delivery. Membranes in these two were ruptured at the end of the first stage of labor. Labor lasted approximately three and one-half hours in 3 and sixteen hours in the fourth. Associated anatomic lesions demonstrable at autopsy were petechiae of the thoracic viscera (two) and clubfeet and a cleft palate (one). Fluid measurements in two of the cases were 35 and 37 c.c.

Discussion

The question immediately arises as to whether the excessive meningeal fluid is primary or secondary, i.e., whether it is the cause or the result of the asphyxia arising from inadequate pulmonary ventilation.

Clifford³ believes that the meningeal edema is part of a progressive disturbance which is brought about by inadequate oxygenation of the blood. He has reported 11 infants who died following cesarean section performed for maternal hemorrhage from placenta previa. All infants developed severe respiratory embarrassment, and all but 2 died within thirty-six hours after birth, although no evidence of fetal distress had been noted prior to delivery. He believes that asphyxial changes resulting from interference with placental circulation had occurred before delivery despite the absence of symptoms. He states that the initial stage of generalized congestion which results from asphyxia is soon

The nucleotide nitrogen of the whole blood in various diseases besides the anemias and polycythemias has also been studied by Rothmann¹⁰ and by Allen, Lucia, and Eiler.¹³ In general no alterations in the nucleotide nitrogen were observed which could not be correlated with changes in the red cell or white cell count. There is, however, a suggestion in Rothmann's paper that the blood nucleotides may vary independently of the red cells in gout.

In eclampsia there are rapid changes in the blood uric acid levels. There might be, therefore, some correlation between the blood uric acid level and the blood nucleotide level in this disease which could be observed. Therefore, to ascertain whether or not there is any such relationship between the blood uric acid levels and the blood nucleotides in normal pregnancy and/or in the toxemias of pregnancy the blood nucleotide nitrogen, the blood nucleoside plus free purine nitrogen, and the uric acid were determined in a series of nontoxemia cases and in several cases of toxemia.

Several methods for the quantitative determination of the blood nucleotides have been described^{11, 15-17, 19, 20} or applied to this end¹⁸ by different investigators. The results obtained are summarized in Table I. The type of filtrate used in the analysis is indicated since Kerr and Blish¹⁹ showed that higher values are obtained with trichloroacetic acid filtrates than with tungstic acid filtrates.

TABLE I. NUCLEOTIDE NITROGEN OF HUMAN BLOOD AS DETERMINED BY VARIOUS INVESTIGATORS

NUMBER OF DETERMINATIONS	SEX	FILTRATES	NUCLEOTIDE NITROGEN MG. % (MEAN VALUE)	INVESTIGATOR
6	—	Acetic acid, Sulfo-salicylic acid and uranium acetate	4.17	Tannhauser and Czoniczer ¹⁷
5	—	Folin-Wu	3.9	Jackson ¹⁶
6	F	Folin-Wu	3.2*	Buell and Perkins ¹⁵
11	M	Folin-Wu	3.9*	Buell and Perkins ¹⁵
1	—	Tungstic acid	3.15	Mozolowski ¹⁸
2	—	Acetic acid	3.97	Mozolowski ¹⁸
			5.74	
98**	—	Folin-Wu	3.5	Rothmann ¹⁰
190***	F	Folin-Wu	4.3	Erickson and Okey ²¹
?	—	Trichloroacetic	6.86	Kerr and Blish ¹⁹
?	—	Tungstic acid	3.81	Kerr and Blish ¹⁹
25†	M	Trichloroacetic	6.25*	Buell ¹¹
25††	F	Trichloroacetic	5.5*	Buell ¹¹
93‡	M	Trichloroacetic	5.0	Allen, Lucia, and Eiler ¹³
31§	F	Trichloroacetic	4.9	Allen, Lucia, and Eiler ¹³

*Calculated values based on the assumption that the blood nucleotide is mainly adenylic acid, containing 20.1 per cent nitrogen.

**An average of 98 pathologic cases.

***On 16 women.

†On 9 men.

††On 8 women.

‡On 76 pathologic cases.

§On 26 pathologic cases.

Summary

Among infants who die early in the newborn period of apparently unknown causes, meningeal edema (external hydrocephalus) must be considered as a possible cause. It is most commonly found following delivery by cesarean section. The maternal complications necessitating this method of delivery do not seem to be causative factors. Slightly premature infants are more often affected than those born at term.

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BLOOD NUCLEOTIDES IN PREGNANCY AND IN THE TOXEMIAS OF PREGNANCY*

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IT HAS long been suspected that the hyperuricemia observed in the toxemias of pregnancy might be due to an alteration in uric acid metabolism.¹⁻⁶ However, little is known of the metabolic pathways leading to the formation of or to the destruction of uric acid in man. One is, therefore, forced to make certain assumptions as to the possible pathways of uric acid metabolism in order to study the etiology of eclampsia. Precursors of uric acid might, for instance, be either blood nucleotides, nucleosides, or other purines.

The blood nucleotides were first discovered by Bass,⁷ in 1914, when he presented evidence for the existence of combined purines in human blood. The combined purine was present as a nucleotide, and it was confined mainly to the red blood cells. Adenine seemed to be the principal purine present.

A successful isolation of the nucleotides present in human blood has not been accomplished. However, Jackson,⁸ in 1924, did succeed in isolating a mixture of nucleotides from human blood. After hydrolysis of this product adenine was isolated. It is now generally assumed that adenylic acid is the principal nucleotide present in human blood. The pyridine-adenine dinucleotides are present only in traces.⁹

Although Bass first showed that the nucleotides of the blood were present mainly in the red cells, it remained for Rothmann¹⁰ and Buell^{11, 12} to demonstrate a correlation between the nucleotide content of the whole blood and its hemoglobin content, the hematocrit and the red cell count. Allen, Lucia and Eiler¹³ have also found this relationship to hold except in cases of leucemia.^{13, 14}

*This study was aided by a grant from The John and Mary R. Markle Foundation.

and by Allen, Lucia, and Eiler¹³ in various diseases. Probably this difference is due to the decrease in both the hematocrit and hemoglobin usually observed in the last trimester and at term in normal pregnancy.²⁴ This contention is confirmed by the fact that the average hematocrit was 35.9 in the nontoxemic series and 35.2 in the toxemic series, while the normal nonpregnant hematocrit as given by Buell in her series would be about 42. The hemoglobin at term is usually about 80 per cent.²⁴

TABLE III. NUCLEOTIDE NITROGEN, NUCLEOSIDE PLUS FREE PURINE NITROGEN, URIC ACID NITROGEN AND HEMATOCRIT OF TOXEMIA CASES

CASE	HEMATO- CRIT %	NUCLEO- TIDE NITROGEN MG. %	NUCLEO- SIDE + FREE PURINE NITROGEN MG. %	URIC ACID NITROGEN MG. %	DIAGNOSIS
J. W.	34	3.72	2.04	1.8	Mild pre-eclampsia
C. M.	36	3.64	1.26	1.4	Mild pre-eclampsia
E. A.	30	2.72	1.12	1.41	Toxemia
D. L.	41	3.78	1.26	1.5	Severe pre-eclampsia
H. S.	47	3.10	1.60	1.3	Severe pre-eclampsia
H. S.	—	4.53	1.74	0.9	H. S., 7 days post par- tum
O. P.	36	4.08	—	1.5	Severe pre-eclampsia
M. P.	41	3.24	2.19	1.60	Severe pre-eclampsia
M. P.	—	3.28	0.62	—	M. P., 7 days post par- tum
T. M.	39	4.94	0.84	1.4	Severe pre-eclampsia
P. F.	26	3.24	1.18	1.0	Severe pre-eclampsia
R. L.	36	3.67*	2.49	1.4	Post-partum eclampsia
(J. L.)	32	(3.95)†	4.02	3.4	Ante-partum eclampsia
H. M.	36	3.88‡	1.76	1.7	Fulminating eclampsia
(H. M.)	—	(3.36)§	1.18	1.7	Immediately post par- tum
H. M.	25	3.22	1.03	1.3	H. M., 4 days post par- tum
Mean	35.3	3.65			

*Delivery 7:12 A.M. Convulsion at 12:00 NOON. Blood sample at 12:15 P.M.

†Last convulsion 8:50 A.M. Blood sample at 10:00 A.M.

‡Last convulsion at 5:30 P.M. Blood sample at 7:15 P.M.

§Delivery 6:30 A.M. Blood sample 11:00 A.M.

Figures in parentheses were not included in the statistical evaluation of the data.

There seems to be no correlation between the blood uric acid level and the blood nucleotide level either in the nontoxemic or in the toxemic series. In this respect specific cases are of interest. Case J. F. in the nontoxemic series had an extremely low blood uric acid and yet here blood nucleotide nitrogen was within normal limits. In the toxemic series, it can be seen that the blood uric acid in Cases M. P., J. L., and H. M. were all quite high while the blood nucleotide nitrogen was again within normal limits.

These data agree in general with those obtained by previous investigators^{10, 13} who have not found any significant variation in the blood nucleotides except in those diseases which involve the cellular elements of the blood. It is of interest to note in this connection that the concentration of the pyridine-adenine dinucleotides remains constant within the red cell even in pellagra.⁹

The nucleoside plus free purine nitrogen is of the same order of magnitude and in most cases approximately equals the value for the uric

Materials and Methods

All the cases studied were in-patients in this clinic. The nontoxemias were mainly cases of normal pregnancy. Included in the series, however, is one case (J. F.) of vomiting in the ninth week of pregnancy (of interest because of the extremely low blood uric acid level); one case of hypertensive disease (F. P.); and one case of cardiac disease with inactive pulmonary tuberculosis (M. M.). Except for J. F., they were all in their last week of pregnancy when the blood samples were taken.

Blood samples from the toxemia cases were taken at the height of the disease and in a few cases samples were taken again during the puerperium.

The blood was removed from an arm vein in the usual manner and was transferred to a small bottle containing oxalate. Ten milliliters of blood were then immediately added to 40 ml. of 10 per cent trichloroacetic acid. This mixture was shaken and allowed to stand for twenty minutes before it was filtered. Blood nucleotide and blood nucleoside plus free purine nitrogen were determined on an aliquot of this filtrate by the method of Kerr.²⁰ Simultaneous uric acid determinations were made on tungstic acid filtrates by the direct method of Folin.²² The hematocrit was determined by the Wintrobe²³ method.

Results and Discussion

The results of these analyses are summarized in Tables II and III. The mean value for the blood nucleotide nitrogen in normal pregnancy during the last week of pregnancy is 3.48 ± 0.67 (σ) mg. per cent, while in the toxemias of pregnancy the mean value is 3.65 ± 0.58 (σ). The t value for the difference between the means is 1.83. The t value should be greater than 2.06 for the difference between the two means to be significant.

These values for the blood nucleotide nitrogen are significantly lower than those reported by both Buell¹¹ in normal nonpregnant women

TABLE II. NUCLEOTIDE NITROGEN, NUCLEOSIDE PLUS FREE PURINE NITROGEN, URIC ACID NITROGEN AND HEMATOCRIT OF NONTOXEMIC PATIENTS

CASE	HEMATOCRIT %	NUCLEOTIDE NITROGEN MG. %	NUCLEOSIDE + FREE PURINE NITROGEN MG. %	URIC ACID NITROGEN MG. %
I. S.	39	3.89	0.73	0.90
J. F.	39	3.11	—*	0.13
M. B.	35	3.22	0.59	0.71
F. P.	46	4.44	1.04	1.00
C. M.	38	3.22	0.95	0.90
F. P.	46	4.14	0.53	0.90
C. R.	32	4.06	1.42	1.02
E. V.	36	3.14	0.70	0.69
A. B.	39	3.58	0.84	0.90
D. R.	35	1.76	0.84	0.90
C. L.	38	3.42	1.26	1.31
A. G.	35	3.87	0.70	0.85
M. M.	41	3.42	0.70	1.42
Mean	35.9	3.48		

*Very low.

THE INCIDENCE OF THE RH FACTOR AND ERYTHROBLASTOSIS FETALIS IN CHINESE*

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RECENT studies have revealed that iso-immunization of the Rh- mother by the dominant Rh factor of fetal blood is the essential feature in the pathogenesis of erythroblastosis fetalis, in at least 90 per cent of the cases. The statistical data indicate that the source of the intrauterine hemolysis of fetal blood, which is responsible for the clinical and pathologic criteria of erythroblastosis fetalis, is the action of maternal immune anti-Rh agglutinins on the susceptible Rh+ fetal blood.^{1, 2}

There is already evidence that the incidence of the Rh factor is different in the white and in the colored races. Thus, with a particular human anti-Rh serum, there are 15 per cent Rh- white individuals in contrast to values varying from 5 to 8 per cent among colored individuals.^{3, 4} All other factors being equal, but particularly the capacity to produce anti-Rh agglutinins, one should expect to find a greater incidence of erythroblastosis fetalis in white than in colored infants.³ This observation seems to correspond with clinical observations of Potter,⁵ and our own recent experience with a vast clinical material. In post-mortem studies of fetal and neonatal conditions, Potter found that the incidence of erythroblastosis fetalis was 2.1 per cent and 0.7 per cent for the white and colored races respectively.

Recently an opportunity presented itself to study the distribution of the Rh factor in Chinese living in New York City. In the course of a discussion, one of us (H. W.) expressed the opinion that this condition is probably rare among Chinese infants. If this could be shown to be correct, one should expect to find a very low incidence of Rh- individuals in a random Chinese population. This was confirmed in a study of 150 Chinese persons residing in New York City, only one of whom was Rh-. The contrasting distribution of Rh+ and Rh- reactions among white and Chinese as tested with three varieties of human anti-Rh sera is given in Table I.

TABLE I. AGGLUTINATION REACTIONS WITH HUMAN ANTI-RH SERA

NUMBER TESTED	ANTI-RH ₁ , ₂		ANTI-RH ₁		ANTI-RH ₂	
	+	-	+	-	+	-
334 White	87.0	13.0	85.0	15.0	73.0	27.0
150 Chinese	99.3	0.7	99.3	0.7	93.0	7.0

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†Fellowship Student of the American Bureau for Medical Aid to China.

acid nitrogen obtained by independent determinations of the uric acid by the Folin direct colorimetric method. Assuming that the methods used are sufficiently reliable, it would appear that nucleosides and purines other than uric acid are present in very small quantities in human blood.

Summary

The average blood nucleotide nitrogen in 12 cases of nontoxemic pregnancy with an average hematocrit of 36 per cent was 3.48 mg. per cent. There was no significant difference between this mean and the average blood nucleotide nitrogen determined in 12 cases of toxemias of pregnancy. The nucleoside plus free purine nitrogen was in most cases approximately equal to the uric acid nitrogen.

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incidence of erythroblastosis fetalis also in American Indians, but clinical evidence to support this view is still to be supplied.

The bloods of Chinese and pure-blooded Indians, however, differ in the incidence of reactions obtained with the anti-Rh₂ serum. This is indicated in the results shown in Table II.

TABLE II

AUTHOR	RACE	NO. OF INDIVIDUALS	PER CENT	
			+	-
Levine et al. ²	White	334	73	27
Landsteiner et al. ¹¹	Indians	69	58	42
Levine and Wong	Chinese	150	93	7

As already stated, the anti-Rh₂ serum is not as significant for the diagnosis of erythroblastosis fetalis and for the prevention of intra-group transfusion reactions as the anti-Rh_{1, 2} or anti-Rh₁ sera. However, these findings as well as these given in Table III are of considerable interest from an anthropological viewpoint.

The bloods of the Chinese individuals were tested also for the incidence of blood groups, subgroups and the factors M and N. For comparative purposes the corresponding distribution in a white population is also reported.

TABLE III

	WHITE	CHINESE
O	45.0	30.0
A	41.0	34.0
B	10.0	25.3
AB	4.0	10.7
M	29.2	23.3
N	21.2	22.0
MN	49.6	54.7

Of the 67 Chinese bloods of Groups A and AB, all but 9 were tested for the subgroups.* Only two of the 58 bloods, both in Group AB, were found to belong to subgroup A₂. In contrast to the low value of 3 per cent A₂ are the corresponding figures of 37 per cent for colored and 14 per cent for white individuals.¹²

Summary and Conclusion

Hitherto studies on the distribution of the blood groups and other blood factors in various races had academic interest only. However, this state of affairs is considerably altered by the findings presented on the correlation of the incidence of erythroblastosis fetalis and Rh negative reactions obtained with anti-Rh serum_{1, 2} or anti-Rh₁. The possibility of this relationship for the colored and white races was already suspected but it is definitely established on the basis of the more striking differences between white and Chinese population.

*These bloods were tested in four batches. One of these containing 9 individuals of Groups A and AB was not tested for the subgroups.

In agreement with Landsteiner and Wiener the terminology used in Table I is employed for the differentiation of the three varieties of human anti-Rh sera. It is based on the observation of Levine⁶ that the anti-Rh serum_{1, 2} contains more than one antibody.

As indicated elsewhere,² anti-Rh_{1, 2} or anti-Rh₁ sera are of far greater significance for the diagnosis of erythroblastosis fetalis than the anti-Rh₂ serum. Using the anti-Rh₁ serum which may be considered as standard, Rh- individuals are 21 times less frequent in Chinese than in white individuals. Accordingly, this observation serves as a basis to support the contention that erythroblastosis fetalis is very rare among Chinese infants. A search of the literature, indeed, reveals only one genuine case of erythroblastosis fetalis in a Chinese infant reported in 1932 by Ku and Li.⁷ The files of the *Chinese Medical Journal* from 1916 to date fail to reveal the report of any other proved cases.

Further support for the view that erythroblastosis fetalis is very rare among Chinese infants could be obtained from the experience of Drs. N. J. Eastman⁸ and U. Eno.⁹ In the six years of his experience at the Peiping Union Medical College covering 4,000 deliveries, Dr. Eastman "saw no cases which were recognized as erythroblastosis fetalis," and he states further that none were observed in 3,000 additional deliveries in the four years subsequent to his stay in China. Dr. Eastman writes: "Of course, the question can be raised as to whether some instances of erythroblastosis fetalis were not overlooked. This is doubtless a possibility, but I believe that clear-cut examples of fetal hydrops could not have escaped our attention. In other words, my experience would be in keeping with your findings."

The experience of Dr. U. Eno, Professor of Obstetrics at the Woman's Christian Medical College in Shanghai, may also be quoted: "Mild jaundice of the newborn is very common in China, but no case of erythroblastosis fetalis was diagnosed or suspected in a series of 10,000 deliveries over a period of eleven years at the Margaret Williamson Hospital. This refers to the three well-recognized clinical forms of erythroblastosis fetalis: fetal hydrops, icterus gravis and anemia of the newborn."

Based on the incidence only of fetal hydrops of 1:1,348 deliveries as given by Javert,¹⁰ one should expect at least 12 cases among 17,000 deliveries, the combined experience of Drs. Eastman and Eno. The incidence of all forms of erythroblastosis fetalis in New York is given as one in 400 deliveries, so that one may expect to observe more than forty cases in 17,000 deliveries. Granting that the milder forms of icterus gravis or anemia may have been overlooked, this should certainly not hold for fetal hydrops and the more severe forms of icterus gravis, the diagnostic criteria for which are, as a rule, clear-cut.

In a recent paper, Landsteiner, Wiener and Matson¹¹ found only one out of 120 full-blood American Indians to be Rh- in tests with standard anti-Rh sera. Accordingly, one should expect a correspondingly low

presence or absence of a history of previous failure. Of those that decompensated before, 75 per cent had cardiac failure when pregnant, as compared to a 14.1 per cent incidence of cardiac failure in the group who had never before experienced decompensation.

From the study of this first group of 345 cases several other conclusions relative to the management of heart disease in pregnancy were reached. It appeared that the greatest incidence of failure occurred in the seventh and eighth months. It was found that the morbidity and mortality rates following cesarean section were significantly higher than following vaginal delivery, and that decompensation in labor was a rarity.

Thus from Jan. 1, 1939, the cardiac clinic in the Margaret Hague Maternity Hospital has been conducted on the following basic principles:

1. All pregnant women with heart disease are examined at frequent intervals and urged to spend several hours in bed every day.

2. All patients whose measure of functional capacity prior to the pregnancy places them in Grades III or IV are hospitalized at their first visit to the clinic, regardless of how well they may seem to be at the time; and kept at absolute bed rest for the remainder of the pregnancy.

3. All patients who give a history of previous decompensation are treated as Grade III and IV cardiacs; hospitalization at absolute bed rest for the remainder of the pregnancy, with no attention paid to their functional capacity at the time first seen.

4. The cardiac patient who is more than twenty-five years of age is observed at weekly intervals. At the first sign of any decrease in cardiac reserve she is hospitalized and placed at absolute bed rest for the remainder of her pregnancy.

5. Special care was taken and increased bed rest ordered in every cardiac patient during the sixth, seventh, and eighth months.

6. Surgical intervention was considered contraindicated. Labor was allowed to occur spontaneously and cesarean section resorted to only when obstetric indications existed.

The purpose of this paper is to compare the result of this type of management to that previously enforced. For this study we have divided our cases into three groups, clinic cases, non-clinic cases, and private cases. The clinic cases, a total of 157 patients, include all pregnant women with rheumatic heart disease who registered at the Margaret Hague clinic at any time prior to delivery. The nonclinic cases, a total of 11, are composed of that group of women who did not register at the hospital until labor began or who were found to be in cardiac failure at their first ante-partum clinic visit. The private cases made up a total of 55 patients. Thus these three groups include every pregnant patient with rheumatic heart disease seen at the hospital from Jan. 1, 1939, to Aug. 1, 1942.

In the clinic group of 157 consecutive cases there occurred four failures, an incidence of 2.5 per cent as compared to an incidence of 22.3 per cent in the first series. Only one death occurred in this group, an

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RHEUMATIC HEART DISEASE

A Controllable Complication of Pregnancy

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IN 1941 an analysis of 345 cases of rheumatic heart disease complicated by pregnancy was reported.¹ This series included all the cases seen at the Margaret Hague Maternity Hospital from January, 1933 to January, 1939. A second series including all the cases seen from January, 1939, to August, 1942, has recently been completed. This latter group comprises 223 cases.

In both series we followed the New York Heart Association classification as follows:

- Grade I: Patients with cardiac disease and no limitation of physical activity.
- Grade II: Patients with cardiac disease and slight limitation of physical activity.
- Grade III: Patients with cardiac disease and marked limitation of physical activity.
- Grade IV: Patients with cardiac disease who are unable to carry on any physical activity without discomfort.

From the analysis of the first series, there emerged three prognostic aids. We felt that it was possible to foretell fairly accurately which patient with heart disease will fail unless adequate bed rest is enforced. First, the functional capacity of the heart in the nonpregnant state is of great importance. In the first series 83 per cent of the failures occurred in the badly incapacitated groups, Grades III and IV, while only 17 per cent of the failures were in the comparatively well-functioning Grades I and II. Second, an equally important aid is the patient's age; 42.6 per cent of the pregnancies in women over thirty years of age were complicated by cardiac failure as compared to 16.1 per cent in the group under thirty. A third significant aid in prognosis is the

much emotional stress. Response to therapy was good. Spontaneous and uneventful labor occurred at term.

This failure was an unexpected and probably an unavoidable occurrence.

CASE 4.—M. D. (History 1145), aged 35 years, had rheumatic heart disease, enlarged heart, mitral insufficiency and stenosis, Grade III prior to this pregnancy. She was hospitalized at her first clinic visit in relatively good condition. Uncooperative to an extreme degree, she signed her release after five weeks of bed rest, did not report to clinic, and returned to the hospital six weeks later. A spontaneous two-hour labor was followed an hour later by acute left ventricular failure which responded quickly to therapy.

We anticipated trouble in this type of case and possibly could have avoided it. We believe that three of these failures were preventable.

In the private series of 55 patients there were 19 failures, an incidence of 34.5 per cent, and 5 deaths, or 9.1 per cent. While we do not intend to compare the private and clinic groups, we feel that the record made by the private doctor is a bad one. Many of the patients in the private series did not know they had heart disease; scarcely any received adequate bed rest; practically all revealed in their histories that their cardiac reserve had been decreasing gradually for weeks or months before frank decompensation had occurred, but the signals were unheeded. In the first series reported in 1941, the failure rate in the private cases was 45.2 per cent. Slight, if any, improvement has taken place.

The nonclinic group of 11 cases needs little comment. Six failures, 54.5 per cent, and two deaths, 18.2 per cent, occurred.

Since completion of the analysis of the first series of cases it has been the policy at the Margaret Hague Maternity Hospital to manage the labor of pregnant women with heart disease on the basis of obstetric

TABLE II. CESAREAN SECTION, PRIVATE VS. CLINIC

GRADE	TOTAL	VAGINAL DELIVERY	CESAREAN SECTION
<i>Clinic</i>			
I	111	109	2
II	25	25	0
III	20	20	0
IV	0	0	0
	156	154	2
		98.7%	1.3%
Died undelivered 1			
<i>Private</i>			
I	40	35	5
II	9	7	2
III	3	3	0
IV	1	0	1
	53	45	8
		84.9%	15.1 %
Died undelivered 2			

incidence of 0.64 per cent as compared to an incidence of 3.47 per cent in the first series.

TABLE I. PRIVATE, CLINIC, NON-CLINIC CASES

	NONCLINIC	PRIVATE	CLINIC
Total	11	55	157
Failed	6, 54.5%	19, 34.5%	4, 2.5%
Died	2, 18.2%	5, 9.1%	1, 0.64%

We believe that several of the cardiac failures could have been avoided and therefore include a brief summary of the histories of these cases.

CASE 1.—C. S. (History 41307), aged 24 years, para i, gravida ii, had rheumatic heart disease with enlarged heart, mitral stenosis and insufficiency, Grade III prior to this pregnancy, and a history of decompensation in her first pregnancy. At the first clinic visit in the fifth month of her pregnancy, this patient was hospitalized and placed at absolute bed rest although her condition at the time seemed excellent. Her course in the hospital was so good that an order was left to "allow bathroom privileges." It should be stressed that this procedure was contrary to our general rules. Acute left ventricular failure occurred during the thirtieth week of this pregnancy. Response to therapy was good, compensation returned rapidly and spontaneous uneventful labor occurred ten weeks later.

CASE 2.—McN. (History 16727), aged 32 years, had rheumatic heart disease, enlarged heart, mitral insufficiency and stenosis, Grade III prior to this pregnancy, a history of previous decompensation. This patient, too, was admitted to the hospital in good condition at her first clinic visit in the third month of her pregnancy. Absolute bed rest was enforced for three months. This patient and Case 1 were in the hospital at the same time. This patient, too, was allowed "bathroom privileges" and she, too, failed at the beginning of the eighth month, an acute left ventricular failure, and died within twenty-four hours.

These two cases were grouped together because their histories are quite similar. They were in the hospital at the same time and received the same management. It was determined later that both patients had been allowed out of bed much more than the "bathroom privileges" had intended. Whether or not these failures could have been prevented is impossible to say, but an element of doubt exists and since this experience no compromise on bed rest is accepted. Absolute bed rest is strictly enforced.

CASE 3.—J. R. (History 43373), aged 22 years, had rheumatic heart disease, a small heart, mitral insufficiency, and stenosis, Grade I prior to this pregnancy. This patient was seen on a routine clinic visit and judged to be doing well. One week later, in the sixth month of her pregnancy, she was admitted in acute cardiac failure. The history revealed a day-long argument with her mother-in-law accompanied by

3. Heart disease is no indication for cesarean section. The two sections performed in the clinic series of 157 cases were on the basis of obstetric indication.

4. Considering a previous report of 345 cases together with this series of 223 cases, in which no therapeutic abortion was performed, it is probable that practically every pregnancy encountered in a patient with heart disease can be brought to a successful spontaneous termination, if adequate prenatal care is instituted and if absolute bed rest is enforced when indicated.

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126 GIFFORD AVENUE

CERVICAL SECRETION IN CHRONIC GONORRHEA IN THE PROSTITUTE

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IT IS well known that in the female chronic gonorrhea is sometimes difficult and occasionally impossible to diagnose. The so-called "stigmata" of chronic gonorrhea in the lower genital tract of the female are absent in some cases which are bacteriologically positive for the gonococcus. The majority of the cases of chronic gonorrhea in the female do, in our experience, bear clinical evidence of infection, though these clinical findings are not pathognomonic of gonorrhea and when present before treatment, may persist after gonococci have disappeared from the secretions.

The diagnosis of gonococcal infections by means of cultures is a great advance, but the culture method also has definite limitations, especially in chronic gonorrhea.

In 1942, a detailed clinical and bacteriologic study was made of the discharges from the cervix and urethra of 81 women, all prostitutes, who had been sent into the Kingston Avenue Hospital for the treatment of gonorrhea.

Material

The venereal disease service of the Kingston Avenue Hospital receives patients who have been found gonococcus positive by the Health Department. Because of their occupation (prostitutes), they have been forced to enter the hospital for treatment to render them noninfectious. The diagnosis of gonorrhea had been established in each case by a positive culture report from the Routine Gonococcus Culture Labora-

indication, essentially as though the women were not suffering from heart disease. In short, heart disease "per se" is not an indication for cesarean section. In the present series of 223 cases, 10 sections were performed, an incidence of 4.6 per cent. However, the figures are more revealing when the private and clinic cases are compared.

Of the total of 156 clinic cases (the patient who died being undelivered), two sections were performed. One was considered necessary by the attending obstetrician in an elderly primipara with cephalopelvic disproportion. This patient was a well-compensated Grade I cardiac. The other was performed as an elective procedure at thirty-seven weeks' gestation because of toxemia of pregnancy. This patient was a well-compensated Grade I cardiac, a primipara with a breech presentation. Thus of the clinic series 98.7 per cent were delivered vaginally and 1.3 per cent by cesarean section, the latter by reason of obstetric indication.

Of the 53 private cases, two having died undelivered, 8, or 15.1 per cent, were delivered by the abdominal route. Two of these were performed at the moment of death in an effort to save the infants and should be discounted; 2 others were indicated by cephalopelvic disproportion; 1 was done for placenta previa; and 1, the Grade IV cardiac, was a previous cesarean section with twins and an embarrassing polyhydramnios in the present pregnancy. This leaves only 2 sections done for so-called cardiac indications. However, 4 other cesarean sections were performed with heart disease as the indication, but these could not be included in this analysis, since there was no good evidence on the chart to show whether or not organic heart disease existed. Thus at least 6 women out of 57 cases received operative interference by the private physician under the indication of heart disease.

We wish to emphasize that no patient in this entire series had her pregnancy terminated in the early months by medical or surgical means. In the clinic group all pregnancies were allowed to go to term; 9 labors were premature spontaneously, and there was one spontaneous abortion.

Summary and Conclusions

1. Two hundred twenty-three cases of pregnancy complicated by heart disease are reported.

2. A system of management of heart disease in pregnancy is briefly outlined. Absolute bed rest for certain classes of cardiac patients is stressed. By this means alone the incidence of decompensation in pregnant women with heart disease has been reduced from 22.3 per cent to 2.5 per cent, 4 cases out of the total of 157; and 3 of these failures may have been preventable. The mortality rate has dropped from 3.5 per cent to 0.64 per cent. If only part of the difference between the failure incidence in private and clinic cases, 34.5 per cent to 2.5 per cent, and if only part of the difference in mortality rates between these two groups of cases, 9.1 per cent to 0.64 per cent, is due to financial difficulties encountered by application of this therapy in private cases, some plan must be instituted by maternity hospitals and the associated communities to overcome such difficulties. However, the private doctor plays a most important part, too, and his responsibility in this condition must be stressed.

TABLE I. VARIATIONS IN CERVICAL DISCHARGE (WITHOUT TREATMENT)

	AD- MITTED	2/12 Prof.*	2/13 Scant	2/14 Scant										
1. L. G.	2/11													
2. W. H.	5/4	2/12 Prof.*	2/13 Scant	2/14 Scant	5/13 Mod.	5/15 Scant								
3. E. K.	4/25	5/5 Scant	5/6 Prof.	5/11 Prof.	5/4 Mod.	5/6 Prof.								
4. M. R.	2/18	4/27 Scant	4/29 Mod.	5/1 Mod.										
5. M. G.	3/2	2/19 Prof.	2/20 Mod.	2/21 Scant										
6. A. C.	5/4	3/2 Mod.	3/5 Scant	3/11 Scant	3/14 Scant	3/23 Mod.	3/25 Scant	3/30 Prof.	3/31 Prof.					
7. B. C.	4/7	5/5 Prof.	5/6 Prof.	5/11 Prof.	5/13 Scant	5/15 Prof.								
8. E. H.	3/26	4/8 Prof.	4/10 Mod.	4/13 Mod.	4/15 Mod.	4/17 Scant	4/20 Scant	4/17 Prof.	4/20 Scant	4/22 Scant	4/24 Prof.	4/25 Scant	4/27 Prof.	

*Mod., moderate. Prof., profuse.

tory of the New York City Department of Health. No patient was sent in on a diagnosis of "clinical gonorrhea" or on positive smears alone.

Each of these patients had been examined gynecologically by a Health Department physician for clinical evidence of venereal infection. Twenty-four of the 81 cases, or 30 per cent, had been recorded on the basis of this examination, as clinically positive for gonorrhea. From this single clinical examination, it appears that 70 per cent of these proved cases of gonococcal infection had no clinical signs of gonorrhea.

At the Kingston Avenue Hospital a gynecologic examination of each patient was made at least three times weekly. One of these examinations was made by the resident gynecologist, one by the attendant on service, and a third examination by another member of the visiting staff.

The examination of the urethra Skene's and Bartholin's glands, the uterus and adnexa, was performed in the usual manner but need not be described here. Because it is the cervix which is most often the seat of gonococcal infection, and the urethra, Skene's and Bartholin's glands are less often involved, we will confine this report to our observations of the secretion of the cervix. We employed the following procedure in obtaining cervical secretion for examination: The cervix is exposed by means of a bivalve speculum, and the appearance of the os, the quantity and nature of secretion therefrom and also of vaginal secretion, if any, is noted. The external os is wiped clean with cotton balls. The blades of the speculum are then caused to come together compressing the entire vaginal portion of the cervix, and the speculum is drawn downward. Any secretion in the cervical canal is thereby forced out and is available for study.

The staff repeatedly examined cases together so as to arrive at an agreement as to descriptive terminology. The quantity and character of the cervical secretion was carefully observed at each examination. The quantity was designated as profuse, moderate, scant, or absent. In character, it was mucoid, purulent, or, in most cases, mucopurulent. In each case a saline suspension of the vaginal secretion was examined for trichomonads.

Findings Before Treatment

The records of the clinical examinations of some of our untreated cases showed fluctuations from time to time in the character and quantity of the discharge. At times profuse mucopurulent discharge was seen, then a day or two later the discharge might be described as scant, and some days later moderate, or again profuse. Repeated examinations on the same day showed fluctuations in the amount of discharge, but this might be ascribed to the expression of the secretion at the time of the previous examination. On some days there was no clinical evidence of infection, while at other times the evidence was unmistakable. In other cases, profuse purulent discharge was found persistently.

Of the 81 cases, in 58 (71.6 per cent) there was found at one time or another a profuse mucopurulent discharge from the cervix.

In 11 (14 per cent), the discharge was described as moderate. Therefore, 85 per cent of our cases repeatedly examined were found to have either moderate or profuse mucopurulent discharge from the cervix. In 12 cases scant or no abnormal cervical discharge was found at any of our examinations.

not in any way correlated to the occurrence of negative cultures. There were patients who yielded negative cultures after an interval of two days and others with positive cultures after more than thirty days. This fluctuation may have been due to the variation in the length of the infection. All were cases of chronic gonorrhea, but no accurate data on the duration of the infection could be obtained. It may be assumed that the women were examined at different stages of the disease. This is one of the many factors that may explain the decrease in the number of positive findings on re-examination. Another is the fact that for obvious reasons, these patients were greatly interested in concealing their infection and probably used various antiseptic substances, such as intravaginal soap, etc., which might have influenced the positive bacteriology of the cervix.

Treatment

On our service, gonorrhea is treated by means of sulfathiazole by mouth, 60 gr. daily for seven days. No local treatment is given and no douches permitted.

A. Clinical Results

Of 58 patients who had profuse mucopurulent discharge from the cervix before sulfathiazole treatment, 25 (43 per cent) were still noted to have profuse mucopurulent discharge three weeks after the end of treatment, although 3 consecutive post-treatment cultures taken at weekly intervals had been reported negative. Twelve (20 per cent) of the 58 who had profuse mucopurulent cervical discharge before treatment had moderate mucopurulent discharge three weeks later, although 3 consecutive post-treatment cultures were negative. Thus 37 of these 58 patients (63 per cent) with profuse mucopurulent cervical discharge, although negative bacteriologically, had not become negative clinically.

Eleven patients who entered the hospital with moderate mucopurulent cervical discharge were noted to have but scant discharge three weeks after chemotherapy was terminated. Of 12 patients who had scant or no discharge before treatment, although their cultures had been positive, none had discharge three weeks later.

B. Bacteriologic Results

Apparent bacteriologic cure was achieved in 64 of the 65 patients. The remaining patient was resistant to sulfonamides and was finally cured after fever therapy.

At the onset of the study, smears and cultures were taken from the urethra and cervix every second day for a period of three weeks after termination of sulfathiazole therapy. Later this schedule was changed to six smears and cultures over a similar period. Provocatives of 1 per cent and 3 per cent zinc sulfate and 5 per cent silver nitrate were used but without any apparent success in increasing the positive findings.

The bactericidal test developed by the Gonococcus Research laboratory which determines the in vitro reaction of gonococcus strains to sulfathiazole was performed on 23 of the 39 gonococcus strains isolated from infected patients. Nineteen showed susceptible strain in vivo and vitro. The strain obtained from a clinically resistant patient showed resistance in the test tube also. There were 3 intermediate strains of patients who responded to treatment.

Clinical Examination

A single examination just before admission to the hospital had revealed clinical evidence of infection in only 30 per cent of our culturally positive cases of gonorrhea, as compared to 85 per cent when the patients were repeatedly examined while in the hospital.

There was a close correlation between the amount of gross cervical discharge and the number of pus cells in the smear. There were only four exceptions to this: In three cases the gross discharge was moderate while the number of pus cells was large. The fourth case showed profuse mucoid discharge with a complete absence of leucocytes on microscopic examination.

Gonococcus culture examinations are used not only for the diagnosis of gonococcal infections but also in the determination of cure. Since only culture positive cases are sent into Kingston Avenue Hospital for the treatment of gonorrhea, we have had the opportunity to evaluate the culture method in a group of proved cases of chronic gonorrhea.

In 1940, we took cultures for the gonococcus from a series of cases immediately after admission and before the institution of treatment. Only 35 per cent of these cultures were reported positive. The cultures were repeated in those reported negative on the first examination, and the positives were increased to a total of 50 per cent. In other words, two consecutive cultures were negative, in the absence of treatment, in half of our newly admitted proved cases of chronic gonorrhea. The following year a similar study was made by another bacteriologist in our Laboratory. Only 55 per cent of positive reports were obtained by repeated culture examinations (varying from two to three in number) of untreated patients.

In the spring of 1942, with the collaboration of Dr. Alfred Cohn of the Gonococcus Research Laboratory of the New York City Department of Health this subject was further investigated.

During the period from February 9 to June 1, 1942, 81 female patients with culture positive for gonorrhea were examined. Sixteen of these were excluded from the report because of (1) early release from the hospital obtained through the Director of the Social Hygiene Division, (2) treatment received prior to hospital admission, (3) lack of cooperation on the part of the particular patient.

As noted previously, all 65 patients had been found culturally positive for gonorrhea by the Gonococcus Routine Laboratory of the New York City Department of Health. When re-examined on admission to the Kingston Avenue Hospital (all specimens for this study being sent to the Research Laboratory for culture), only 39 (60 per cent) were found to have positive cultures. Since this figure includes 6 cases which were positive only on the urethral culture, only 33, or 50.7 per cent, were found positive on cervical cultures alone. Of the total of 47 positive cervical cultures obtained from these 33 patients, 10 were accompanied by positive smears, 2 by suspicious, and 35 by negative smears, which again shows cultures much more accurate than smears. Only one positive cervical smear was observed where the corresponding culture was negative. Of the 31 positive urethral cultures, 5 were accompanied by positive and 2 by suspicious smears; the remaining smears were found negative.

The interval between the first examination at the House of Detention and the first at Kingston Avenue Hospital varied from two to thirty-three days with an average of 6.8 days. The length of the interval was

THE USE OF SODIUM SULFATHIAZOLE IN THE TREATMENT OF SEPTIC ABORTIONS

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THIS study was made in an effort to accomplish two specific objectives. The first was an attempt to reduce morbidity and mortality in cases of septic abortion by the use of specific drug therapy, along with the routine that had been used prior to the advent of such a drug, and second to reduce the hospitalization period, which is of great importance in dealing with a large charity service.

We began this routine on Jan. 1, 1941, and continued it for one year. All cases admitted to our service were handled in the same manner; our controls being obtained from those admitted to the Tulane service during the year 1940. The following was our method of handling each case.

Procedure

On admission to the ward the patient was prepared for surgery and the senior resident called. This work was handled by the latter of the authors. By him or under his supervision all visible products of pregnancy were removed from the vaginal canal. No attempt was made to remove any products from the cervical canal or the uterine cavity. Pitocin, 1 c.c., was given on admission and whenever necessary for free bleeding. Ergotrate, gr. 1/320, was given every six hours for three days. Vaginal packing was used only for profuse uterine bleeding which could not be controlled by other measures. When used, the pack was always removed within twenty-four hours. When such a procedure was to be carried out, the patient was placed in the Sims or knee-chest position, and cotton balls, saturated with saline, were used, placing them against the cervix in a concentric manner.

Laboratory work included urinalysis, blood and cervical cultures, and complete blood picture. If the total red blood count was below 3,500,000, the patient was given a transfusion of from 500 to 1000 c.c. of whole blood.

The cervical and blood cultures were taken by the bacteriologic department of the hospital, and these results will be shown later.

Sodium sulfathiazole was given only to those proved to be septic, and not alone on history of chills and fever or of instrumentation. It has been our experience that many patients will have a temperature even up to 103° F. on admission; and following the administration of pitocin or the removal of products of pregnancy from the vagina, the temperature will return to normal within twenty-four hours and remain so. For that reason no patient was considered septic until the temperature had remained at 100.4° F. or higher for twenty-four to forty-eight hours. When this condition existed, she was given an initial

Trichomonas vaginalis was found in the vaginal secretion in two-thirds of our cases and remained unaffected by sulfathiazole treatment.

No statement concerning clinical cure can be made from this study, because unfortunately the time of observation after therapy was too short.

Summary

1. A single gynecologic examination just before admission to the hospital revealed clinical evidence of infection in only 30 per cent of a group of prostitutes culturally positive for the gonococcus, as compared to 85 per cent when the patients were repeatedly examined in the hospital.

2. Cultures for the gonococcus were taken before institution of treatment from 65 women with chronic gonorrhea who had had positive cultures just before admission. Only 60 per cent were found positive on repeated culture examinations, while a single culture was positive in only 45 per cent.

3. In view of our findings in untreated cases, the limitations of the culture in the diagnosis of chronic gonorrhea are obvious. A few negative cultures have limited value in ruling out the diagnosis, or as proof of cure.

4. In the clinically positive cases treated with sulfathiazole, 63 per cent still had moderate or profuse mucopurulent cervical discharge when examined three weeks later, although gonococci were no longer found on culture.

5. The greater value of the culture as compared to the smear, in chronic gonorrhea, was again demonstrated.

6. Trichomonads were found in two-thirds of our cases, and persisted in spite of sulfathiazole therapy. The presence of trichomonads should not cause us to overlook a possible gonorrhea.

We express our thanks to Dr. Alfred Cohn of the Research Laboratory of the New York City Department of Health and to Dr. Julius Sass, Pathologist, and Miss Lillian Robbins, Bacteriologist of the Kingston Avenue Hospital for their assistance, without which this study would have been impossible.

hemolysis are called "alpha streptococcus." All others are grouped under the term "nonhemolytic streptococci," which undoubtedly includes several varieties. A markedly pleomorphic streptococcus growing aerobically or facultatively anaerobically was commonly found, for which the descriptive term "diphtheroidal streptococci" was employed.

Anaerobic gram-negative bacilli are not further differentiated in this report. Those isolated appear to belong to the group of nonsporulating obligately anaerobic gram-negative bacilli which Bergey calls "bacteriodes."

Results

TABLE I. RESULTS OF CERVICAL CULTURES IN CLEAN CASES

ORGANISM	ANAEROBIC	AEROBIC
Beta streptococcus	2	1
Alpha streptococcus	3	2
Gram-negative bacilli	38	—
Nonhemolytic streptococcus	76	77
<i>Alcaligenes faecalis</i>	—	2
Diphtheroid	—	49
Diphtheroid streptococcus	—	—
<i>Escherichia coli</i>	—	13
<i>Staphylococcus aureus</i>	—	2
<i>Staphylococcus albus</i>	—	32

TABLE II. RESULTS OF CERVICAL CULTURES IN SEPTIC CASES

ORGANISM	ANAEROBIC	AEROBIC
Beta streptococcus	—	1
Alpha streptococcus	2	—
Gram-negative bacilli	10	—
Diphtheroid	—	11
Diphtheroid streptococcus	—	3
<i>Escherichia coli</i>	—	—
<i>Staphylococcus aureus</i>	—	2
<i>Staphylococcus albus</i>	—	4
Nonhemolytic streptococcus	12	17

There were a total of 124 clean cases that had a positive cervical culture; this representing 78 per cent of the clean cases reported. In the septic cases there were 34 positive cervical cultures, which is 77 per cent of the total number reported. It thus appears that the true present condition and prognosis of the patient could not be ascertained by a knowledge of the cervical culture alone.

TABLE III. RESULTS OF CASES STUDIED

Total number of cases	200
Total clean cases	156 (78%)
Total septic cases	44 (22%)
Total curettements	6 (3%)
Total vaginal packs	3 (1.5%)
Total number of deaths	2 (1%)

As shown in Table III, there were a total of 200 cases studied. Of these, 156 (78 per cent) were clean cases, and 44 (22 per cent) were septic. There were only 6 cases where curettement was found necessary, as compared to a study made in 1940 which revealed the fact that

dose of 3 Gm. of sodium sulfathiazole by mouth and then 1 Gm. every six hours for five or more days. The drug was stopped if red blood cells appeared in the urine, if severe leucopenia developed, or if other signs of severe toxic reaction resulted.

Having adopted a conservative form of treatment in these cases, it was not our practice to perform curettement except in those cases of uterine bleeding that could not be controlled by any other means. When we found it necessary to curette, it was not done unless the patient had never been septic or had been afebrile for one week.

The routine used in obtaining and studying the cultures was obtained from the bacteriologic department of the hospital and is as follows:

For purposes of bacteriologic study two types of specimens were collected: (1) venous blood, and (2) a swab from the cervical canal. For the latter, the patient was prepared as for a sterile vaginal examination, and a sterile speculum was inserted to expose the cervix. Any clots and visible tissue were removed, and the cervix cleaned with sterile sponges. A small swab was inserted into the cervical canal to a depth of about an inch and one-half and placed immediately into a tube of glucose-brain broth.

This medium contains a piece of calf brain tissue and is additionally buffered with a small amount of crushed marble, which also provides an alkaline anaerobic environment in its immediate vicinity. It has been found to support the growth of a wide variety of organisms, including most anaerobes and the more fastidious streptococci and gram-negative bacilli.

After a preliminary incubation of three to four days, the swabs were removed and the broth subcultured to duplicate sets of infusion rabbit's blood-agar plates. One set was incubated aerobically and the other anaerobically in a phosphorus jar for four days. Occasionally smears of the broth culture revealed organisms which did not grow out on the plates, and it was found possible to maintain their viability in brain broth transplants. Distinct colony types were fished from the plates, smeared for microscopic examination, and subcultured appropriately.

Glucose-brain-broth was also inoculated with blood drawn at the same time the cervical culture was taken. Tubes containing 20 c.c. of broth were inoculated with 2 c.c. of blood. In addition, pour-plates were made with glucose-extract-agar. When growth resulted, subcultures and identifications were made in the manner described for cervical cultures. Blood cultures were observed for one month before being called negative.

Certain organisms were seen to predominate and are probably to be regarded as normal flora of the cervix. Like the streptococci of the nasopharynx and the fusospirochetes of the mouth, however, some of them are very likely capable of pathogenic activity when other conditions prepare the way. Since the flora of the cervix has not been adequately studied, to our knowledge, some remarks about the most frequently present bacteria are here appended.

Diphtheroid bacilli were not further differentiated. Organisms are so designated if morphologically and culturally they display the main characteristics of corynebacteriae.

Streptococci were named according to the type of hemolysis produced, or the lack of it. Those exhibiting large clear zones of hemolysis are designated "beta streptococcus." Those producing incomplete or green

TABLE VII. TOXIC REACTIONS

Severe nausea	4 Cases
Severe vomiting	1 Case
Severe headache	1 Case
Leucopenia	1 Case

As will be noted in Table VI, the average amount of sodium sulfathiazole used required five days, following the routine which we adopted. The toxic reactions were relatively uncommon and in only one instance was it necessary to discontinue the use of the drug; this being the patient that developed leucopenia.

TABLE VIII. COMPLICATIONS

Cystitis	1 Case
Cul-de-sac abscess	1 Case
Pyelonephritis	1 Case
Infectious arthritis	1 Case
Generalized peritonitis	2 Cases

The complications occurring in this series are shown in Table VIII. Uneventful recovery was made in all instances, except that of the two cases of generalized peritonitis, these having been discussed in detail previously.

TABLE IX. MORTALITY OF ABORTIONS. CHARITY HOSPITAL 1937 TO 1941

YEAR	ENTIRE HOSPITAL	TULANE	DEATHS ENTIRE HOSPITAL	TULANE DEATHS
1937	1,325	491	22, 1.6%	7, 1.4%
1938	987	392	13, 1.3%	3, 0.7%
1939	927	346	13, 1.4%	4, 1.1%
1940	1,140	419	10, 0.8%	5, 1.1%
1941	957	369	5, 0.5%	2, 0.5%

Table IX shows that the mortality during the past five years has shown a steady downward trend; both for the entire hospital and our own service. The lowest figures for both occurred during the years 1940 and 1941, and we are of the opinion that this has been accomplished through the use of specific chemotherapy.

Summary and Conclusions

We have presented a definite conservative routine for the handling of abortions, with the addition of specific drug therapy in septic cases. By following this routine we have shown that the morbidity, mortality, and length of hospital stay have been greatly reduced. We have also reduced the number of curettements to a minimum.

Cervical cultures were found to be of little value in determining the presence of pelvic sepsis, as an equal number of positive cultures were obtained in the clean cases.

Sodium sulfathiazole therapy gave good results in all cases, irrespective of type organism found.

The Winthrop Chemical Co. supplied the drug. We also wish to acknowledge the assistance given us by Dr. E. M. Moss and staff of the Department of Pathology at the Charity Hospital, New Orleans, La.

in 172 cases of abortion, curettement was done in 24 (13.9 per cent). These were handled, however, by separate members of the staff before a definite routine was established, and might explain the great difference between the two years. However, this number of curettements is not excessive, even where one is following a conservative form of treatment.

The two deaths that occurred were both cases of criminal abortion. The first was that of a patient who was admitted to the hospital in a moribund state and died within twenty-four hours without receiving any specific drug therapy. The second death occurred in a patient who was admitted with generalized peritonitis and severe toxic jaundice. She responded temporarily to sodium sulfathiazole therapy, but died rather suddenly of pneumonia seven days after admission.

TABLE IV. RESULTS IN CLEAN CASES

Average hospital stay	5.4 days
Number of curettements	5 (3.1%)
Number of vaginal packs	2 (1.2%)
Number of cases transfused	28 (17%)
Number of cases admitted to be criminal	11 (7.1%)

The average hospital stay to our knowledge compares favorably to that found in other reports. The small number of patients who were packed is of interest, and in our opinion is what it should be.

TABLE V. RESULTS IN SEPTIC CASES

Average hospital stay	10.1 days
Number of curettements	1 (2.2%)
Number of vaginal packs	1 (2.2%)
Number transfused	20 (45.4%)
Number of cases admitted to be criminal	12 (27.2%)

As shown in Table V, the average hospital stay of septic cases that received sodium sulfathiazole was ten days. In studying a similar number of septic patients who were admitted to the Tulane service during the year 1940, and who did not receive any specific drug therapy, we found that the average hospital stay was thirteen days. Among those patients who received specific therapy, the average duration for the reduction of temperature to normal was accomplished in approximately three days.

The one curettement shown in Table V was performed on a patient who returned to the hospital after completion of her septic course because of recurrence of uterine bleeding. Being afebrile she was curetted and her postoperative course was uneventful.

One vaginal packing was done in this series, because of uncontrollable bleeding in a patient whose red blood count had dropped to 1,200,000.

TABLE VI. AMOUNTS OF DRUG USED

Average amount of sodium sulfathiazole used	24.4 Gm.
Largest amount of sodium sulfathiazole used	72 Gm.
Smallest amount of sodium sulfathiazole used	6 Gm.

Material

This study was conducted at the Jefferson Medical College Hospital on 117 unselected women in labor. These patients were grouped as follows:

Primiparas	92	78.6%
Multiparas	25	21.4%

This corresponds to our ratio of ward admissions in primiparas and multiparas. We felt that we were fortunate in having so large a percentage of primiparous patients, since it is in this group that analgesia and amnesia play their greatest roles.

The youngest patient in our series was 14 years of age and the oldest was 45 years. The individual ages ranged as follows:

AGE	NUMBER OF CASES
14	1
15-20	60
21-25	35
26-30	12
31-35	3
36-40	5
41-45	1

Approximately 92.3 per cent of our patients were under 31 years of age.

Presentation was as follows: 113 cephalic and 6 breech. According to position they were as follows:

L.O.A.	64
R.O.A.	42
L.O.P.	2
R.O.P.	5
Breech	6

Mention should be made concerning some of the complications that have been observed in this group. There was one case of polyhydramnios, one of syphilis, and one of placenta previa of the marginal type.

Administration of the Drug

When this study was undertaken, we were concerned with determining the proper dose, that is, one that would give proper analgesia and amnesia with minimal deleterious effects on the mother and the child. Starting with small doses, the drugs was administered in increasing amounts until the desired therapeutic effect was obtained. This dose was found to fall between 3 and 6 gr., and, after careful evaluation, we determined that the average initial dose of sodium vinbarbital was 4½ gr. As previously mentioned, the dose was adjusted to the patient, and, therefore, some patients received an initial dose of 3 gr. while others required 6 gr. This drug was given and supplemented with scopolamine in most cases.

The initial dose of 4½ gr. of sodium vinbarbital was administered early in the first stage of labor, either when contractions became defi-

VINBARBITAL SODIUM FOR OBSTETRIC AMNESIA AND ANALGESIA

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BECAUSE of the lack of uniformity in the various methods of obtaining obstetric amnesia and analgesia and also the controversy concerning them, this study was conducted to determine a logical routine in alleviating the discomfort and side-effects of parturient women and in providing maximum safety for the newborn.

The excitement which we had experienced in our obstetric service with sodium ethyl (1-methylbutyl) barbiturate and the lack of cooperation with sodium allyl (1-methylbutyl) barbiturate, led to a further search among the barbiturates for a more satisfactory agent. Sodium ethyl (1-methylbutyl) barbiturate, in an initial dose of 6 to 7½ gr., produced a large percentage of cases exhibiting excitement during the first stage of labor; undesirable aftereffects, such as a "hangover," were also frequently experienced. A 3 gr. initial dose of sodium allyl (1-methylbutyl) barbiturate was found to be insufficient in the majority of cases to give a therapeutic response and, although the initial dose was increased, a uniform response was lacking.

Among the more recent developments in the barbiturate field were the delta-1-alkynyl groups of which "Delvinal" sodium vinbarbital* has been made available for general clinical use. The favorable reports in the literature¹⁻⁵ concerning the pharmacologic and clinical investigation of this barbiturate led us to investigate its value as an aid in producing satisfactory obstetric amnesia and analgesia.

Cognizant of the occasional untoward effects of the barbiturates, both immediate and delayed, we endeavored to individualize the dose when administering this drug, adapting the dosage to the patient, rather than the patient to a standard dose. At no time did we feel that it was advantageous to give so large a dose that marked depression might occur.

"Delvinal" sodium vinbarbital, a more soluble barbiturate, is classed as a sedative, hypnotic, and analgesic. Its principal site of action is in the diencephalon. It is rapidly absorbed when administered orally and its action is of short duration. The greater portion of the drug is detoxified in the liver.

*Delvinal vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate. It is prepared by Sharpe & Dohme, Philadelphia, Pa.

Effects on Babies

There were delivered from this group of patients (117 mothers) 119 babies (two sets of twins). Of these, 118 were born alive. There was one stillborn macerated fetus (Wassermann negative). This child was dead before the onset of labor.

The color of the babies born alive was as follows:

Good	98
Fair	18
Poor	2

It was felt that determination of the onset of breathing in these infants was of considerable importance. Therefore, we are listing the time at which the respiratory effort was established: Immediate, 101; slightly delayed, 17; delayed, —. 85.6 per cent of the babies breathed as soon as born. At no time was there any great difficulty encountered in the establishment of respiration in the babies born of this entire group of mothers.

When administering an analgesic agent, a consideration very often ignored or overlooked is the effect it might exert on the conduct and cooperation of that particular patient both during labor and the immediate post-partum period. These side-effects are not only embarrassing, but difficult, and sometimes even dangerous. We have found that our patients responded in about 85 per cent of cases to moderate doses of sodium vinbarbital (3 to 6 gr.) followed one-half hour later by $\frac{1}{150}$ gr. of scopolamine. As previously noted, we individualized the routine administration, and, therefore, some received subsequent doses. One patient received $13\frac{1}{2}$ gr. Yet our patients were not unruly, nor did they need special restraining apparatus. They slept or rested between pains, and in some there was evidenced slight moaning when a uterine contraction occurred. When it became necessary to examine these patients, they responded to orders and were cooperative. It should be mentioned that any patient who receives an analgesic agent should not be left alone, no matter how ideal and apparently foolproof it may be.

When the patient was returned to her bed, following the delivery of the baby and expulsion of the placenta, there was little evidence of the so-called "hangover" that is annoying to the physician and the family of the patient. A large percentage of the patients had several hours' normal sleep following delivery which we feel is of definite value in aiding restorative powers. We feel that this was accounted for by the solubility, lack of toxicity, and rapid elimination of the drug.

Summary of Results

In this series, 117 pregnant women received sodium vinbarbital in the first stage of labor as an agent to produce amnesia and analgesia. Our average, or initial dose, was $4\frac{1}{2}$ gr. followed in one-half hour by $\frac{1}{150}$ gr. of scopolamine. The analgesia was augmented by subsequent doses of the barbiturate in doses of $1\frac{1}{2}$ to 3 gr., which were administered when there was a further need for analgesia. The largest single dose of sodium vinbarbital administered to one patient was $13\frac{1}{2}$ gr. The average total dose was $6\frac{2}{3}$ gr.

nately rhythmical in character or when the cervix showed a 2 cm. dilatation. One-half hour later, when the sedative action was manifest, $\frac{1}{150}$ gr. or $\frac{1}{200}$ gr. of scopolamine was administered hypodermically. This procedure was found to definitely reduce the possibility of excitement during the first stage of labor. Additional doses of sodium vinbarbital were given dependent upon the response of the patient to the initial dose. One and one-half to 3 gr. were administered at one- to four-hour intervals as required to maintain the patient in a zone of effective amnesia and analgesia. Some individuals required $1\frac{1}{2}$ gr. repeated several times; others required 3 gr. less often. The largest total dosage of sodium vinbarbital administered to a single patient in labor was $13\frac{1}{2}$ gr., without any untoward effects to the mother or child. Our average total dose administered was $6\frac{2}{3}$ gr. In several patients the scopolamine was repeated in decreasing doses, such as $\frac{1}{200}$ and $\frac{1}{400}$ gr.

Duration of Labor

The duration of labor was under twelve hours in 54 patients (46.1 per cent), and it was less than twenty-four hours in 87 patients (74.3 per cent). Considering the number of primiparous patients, the duration of labor compares favorably with the average duration of labor.

Method of Delivery

Spontaneous	99 (including 3 spontaneous breech deliveries)
Forceps	17
Breech extractions	3
Episiotomy	43

The number of spontaneous deliveries is evidence that the analgesia and amnesia obtained by the use of sodium vinbarbital did not increase the number of operative deliveries.

Supplemental Anesthesia

Supplemental anesthesia, as indicated in the following table, was administered to 83 patients, or 71.8 per cent, during the second stage of labor.

	PATIENTS
N ₂ O—O ₂	15
N ₂ O—O ₂ (induction) and ether	63
Ether	5
No anesthesia	34

Effects on Mother

It is of considerable importance to evaluate the effect of an analgesic agent on the contractility of the uterus following the birth of the child, and especially after the separation of the placenta and following its expression. In our series we encountered only one case of bleeding that was of considerable magnitude. This occurred in a patient whose pregnancy was complicated by a marginal placenta previa. There was no indication that the use of "Delvinal" sodium vinbarbital increased post-partum hemorrhage.

was absence of restlessness and the so-called "hangover," which is ascribed to many other barbiturates.

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2001 DELANCEY STREET

TESTICULAR TUBULAR ADENOMA IN TWO SISTERS*

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THE extreme rarity of hereditary testicular tubular adenoma and its significance in relation to problems of hermaphroditism and intersexuality appear to justify the publication of the two following cases.

CASE 1.—The patient, a 27-year-old married woman, complained for four months of various insignificant disorders, which according to her opinion were due to excessive smoking. On examination a pelvic tumor was found and an operation advised. The patient never had menstruated, but otherwise was without gynecologic complaints. Sexual intercourse was normal and satisfactory. Her libido was strong and exclusively directed toward the male sex.

Examination.—The stature of the patient, her features, proportions, her hair growth, and the development of her breasts were typically female. There was, however, complete absence of axillary hair and almost complete lack of pubic hair.

Except for a moderate hypoplasia of the major and minor labia, the external genitals were normal. The vagina was of normal length and width and ended blindly. Neither the cervix nor the uterus was palpable. An apple-sized, hard, nodular, movable tumor, however, was palpable in the left lower quadrant, apparently representing the left gonad. The right gonad was not found on examination. The size and shape of the pelvis were normal and of female type.

Operation.—(December 31, 1923.) The abdomen was opened through a low transverse incision. On the left side a mass was found where the left gonad is ordinarily located. It consisted of a whitish, freely movable tumor of about three inches in diameter. On the right side, a similar mass occupying a somewhat higher position was seen. It was ovoid in shape, had a smooth surface and contained two pea-sized palpable nodules. Both gonads were connected by a transverse, arched peritoneal fold extending between bladder and rectum and apparently representing a Muellerian rudiment. Each lateral portion of this peritoneal reduplication contained a nodule about 1 cm. in length and thickness.

*The patients were operated upon in Vienna. The blocks of the pathologic material were cut in the laboratory of Mt. Sinai Hospital and the slides studied under the supervision of Dr. Paul Klemperer, pathologist to the Hospital.

There were 92, or 78.6 per cent, primiparous patients, and 25 or 21.4 per cent, multiparas. The youngest patient was 14 years of age, and the oldest 45 years of age. Approximately 92.3 per cent were under 31 years of age.

In this group, 83, or 71.8 per cent, of the patients received supplemental inhalation anesthesia at the time of delivery.

Length of labor: 54, or 46.1 per cent, were in labor less than twelve hours; 87, or 74.3 per cent, were in labor less than twenty-four hours.

Method of delivery: 99 (including 3 breech presentations) were delivered spontaneously. Forceps were used in 17 cases and there were 3 breech extractions.

Of the babies, 118 were born alive, and there was one stillborn macerated fetus, an intrauterine fetal death.

Of the children born alive, 101 breathed and cried immediately. In 17 there was slight delay; at no time was any great difficulty encountered in obtaining respiratory response.

Conclusion

1. It was found that "Delvinal" sodium vinbarbital was a rapidly absorbed and quickly eliminated barbiturate. In doses mentioned in this paper, it was without harmful effects as far as the mother and child were concerned, although good amnesia and analgesia were obtained in 85.5 per cent of the cases.

2. We feel that this drug should be used in the first stage of labor and supplemented by inhalation anesthesia during the second stage.

3. This drug may be used in patients at different ages, as proved in our group, which varied from fourteen to forty-five years of age. Complications of pregnancy do not contraindicate its use, since it was used in cases of polyhydramnios, syphilis, and placenta previa.

4. Labor was not prolonged by its use, as 46.1 per cent of our patients had labors of less than twelve hours, and 74.3 per cent had labors of less than twenty-four hours, and 99 patients delivered spontaneously.

5. "Delvinal" sodium vinbarbital apparently does not exert untoward effects as far as post-partum bleeding is concerned, since there was only one case of post-partum hemorrhage that occurred in a case of marginal placenta previa.

6. To the 117 mothers there were born 119 children, of which 118 were alive, and one was a stillborn macerated fetus occurring in a case of intrauterine fetal death.

7. There was little difficulty in the inauguration of respiration.

8. We feel that this drug does not exert a depressing effect on the offspring.

9. Patients with good analgesia and amnesia did not become unruly or uncooperative. When general anesthesia was given, it was taken very smoothly, and when the patient was returned to her room there

The occurrence of such striking sexual abnormalities in two sisters suggested the investigation of their heredity. With the help of the two patients, their mother, a grandmother, an aunt, and a physician-relative, valuable information was obtained which enabled me to set up a genealogic tree of their kin. This showed that there were several other members among the kindred who were affected with marked sexual abnormalities, the hereditary taint apparently transmitted from grandmother to her children and grandchildren. There was a preponderance of descendants with feminine appearance.

Pathologic Findings.—The left gonad of the first case was composed of a smaller dark-brown portion and a much larger yellowish, nodular predominantly solid, partly cystic mass. The right gonad showed the same dark-brown color on cross section as the small portion of the left



Fig. 1.—(Case 1.) Section of left gonad, area with canaliculi lined by Sertoli cells. Numerous interstitial cells. ($\times 260$.)

one. The yellowish mass predominant on the left gonad was restricted here to two pea-sized nodules.

In the second case both gonads consisted exclusively of a yellowish tissue which, contrary to the first, was solid only in small areas and riddled by numerous cystic cavities varying in size and filled with colorless fluid.

The microscopic examination proved the brown portion to consist of underdeveloped, but easily recognizable, testicular tissue with typical canaliculi and numerous Leydig cells (Fig. 1). Here and there the interstitial cells were massed in well-defined, dark-stained nodules, resembling the well-known interstitial cell-hyperplasia repeatedly found in cryptorchid testicles.

As a rule, the canaliculi were separated by ordinary loose connective tissue. But here and there small areas of characteristic spindle-shaped

On the top of the right nodule there was a small formation which could be recognized easily as a tubal ampulla. Both gonads were removed, the right one together with the adjacent nodule. In addition an appendectomy was performed.

The postoperative convalescence was uneventful. But several weeks after the operation the patient started to suffer from frequent and severe flushes which gradually diminished and disappeared after several years. She was observed for thirteen years after the operation. Her weight increased only slightly and her sexual reactions remained normal.

CASE 2.—Several months after the operation of the first patient I was consulted by her younger sister. She was 26 years old, married, but had never menstruated. Contrary to her sister she had always been frigid and without sexual desires. Having grown rapidly in her childhood, she was the tallest in her class for some time. But after the thirteenth year her growth became very slow and soon stopped completely. Likewise her breasts developed prematurely and remained stationary after the age of nine. Her past medical history included scarlet fever, typhoid, and bilateral hernioplasty.

Examination.—The patient was 4 feet 7½ inches tall, slightly corpulent (115½ pounds) and strikingly muscular. Her legs were short and slightly curved. The body length was 2 feet 1 inch above the symphysis and 2 feet 6½ inches below. By her short, vigorous stature she resembled a chondrodystrophic individual, but did not show the other typical characteristics of chondrodystrophy. Her features and hair on the head were of female type. The breasts were well shaped, their size corresponding to those of a girl of about sixteen. The axillary hair was absent, the pubic hair was indicated only slightly.

The external genitals were markedly hypoplastic, the mons veneris poor in fat, the labia majora underdeveloped, thin, and flat. The labia minora formed stunted, low projections elevated over the surroundings only in the region of the clitoris. The vagina was 6 cm. in length and ended blindly. Neither cervix nor uterus could be detected. In the cul-de-sac, two ovoid-shaped, nontender tumors were palpable, the left one 3½ by 2½ by 2½ inches, the right one a little smaller.

Operation.—(September 15, 1924.) A laparotomy was performed through a lower midline incision. Adhesions between omentum and the right inner inguinal ring derived from the former hernioplasty were dissected. Both gonads were found changed into partly solid, partly cystic tumors, the left one being 3½ by 2½ by 2½ inches, the right one somewhat smaller. Both tumors were densely adherent to their surroundings. Each gonad was connected by a thick ligament to an archlike peritoneal fold extending transversely between the bladder and rectum, and representing the rudimentary Muellerian ducts. The fold was thin in its central portion, but became thicker laterally, finally forming muscular nodules from which short round ligaments projected into the inguinal canals. Between the right ovarian ligament and the rudimentary uterus, a small rudimentary tube was demonstrable. Both tumors were freed from adhesions and removed.

The convalescence was uneventful. However some weeks after the operation the patient began to complain of unusually severe flushes and sweats, occasionally also of numbness of the hands. These disorders were continuous and responded only slightly to treatment. The flushes continued for thirteen years and have had to be treated continuously by various estrogenic preparations.

often hyalinized or even calcified connective tissue. There were neither Leydig cells nor ovarian stroma cells present within this yellowish tumor. Transitional stages between the typical testicular canaliculi and the canaliculi of the tumor showed the close relationship of the two structures.

The gonads of the second case consisted almost exclusively of the same adenomatous tissue. Only few tubules resembled typical underdeveloped seminiferous canaliculi. Most of the interstitial tissue consisted of ordinary connective tissue with a great tendency toward hyalinization and calcification. Only here and there small areas of closely aggregated spindle cells resembling ovarian stroma were interspersed between the canaliculi.

Discussion

Two patients are described in whose family there were other members with abnormalities of their sexual organs and their secondary characteristics. Though both individuals had a normal female exterior and feminine sexuality, and most parts of their sexual organs were female, their gonads had predominantly male characteristics. They harbored a tumor which undoubtedly, because of its structure and its connection with testicular canaliculi, has to be designated as a testicular tubular adenoma. While the gonads of the second case were almost completely composed of this tumor, the gonads of the first case contained large areas of real testicular tissue with under-developed canaliculi and abundant Leydig cells. On the other hand, scattered areas of ovarian spindle cell stroma prove that the gonads did not consist entirely of male tissue.

Though neither ova nor follicles were found in the gonads the presence of ovarian stroma on the one hand, and the presence of testicular tissue on the other hand, mark the gonads as ovotestes with a great predominance of the male portion. This assumption does not seem to be forced, since in the reported cases of ovo-testis, with or without a tubular adenoma, all possible transitions from functioning ovarian tissue to insignificant ovarian traces, have been met. In any destructive process, the ovarian stroma represents the most resistant part of the ovary and remains as the last residue of the female gonad.

It seems safe to assume that these misshapen gonads were not functionless in these two cases, as their removal was followed by unusually severe and longlasting deficiency symptoms. It is very improbable that the loss of the small remnants of ovarian tissue was responsible for the severe postoperative flushes and sweats in our two cases. One would rather have to attribute these disturbances to the loss of the highly predominant male tissue. Similar disorders were noticed by R. Cadiz and A. Lipsehuetz,¹ Wagner,⁷ and Klaus,⁴ after the removal of testicles in otherwise female individuals. Since such intensive vasomotor and secretory upsets are not seen in males after the removal of testicles, one must

ovarian stroma cells were discernible representing the only demonstrable trace of ovarian tissue (Fig. 2). In spite of a thorough search, neither ova nor follicles could be found.

The yellowish tumor had a different structure (Fig. 3). It consisted of straight or curved ramified cords or canaliculi, lined by a single row of fairly regular high cylindrical, palisade-like epithelial cells. Areas of closely aggregated canaliculi were separated by strands of coarse,

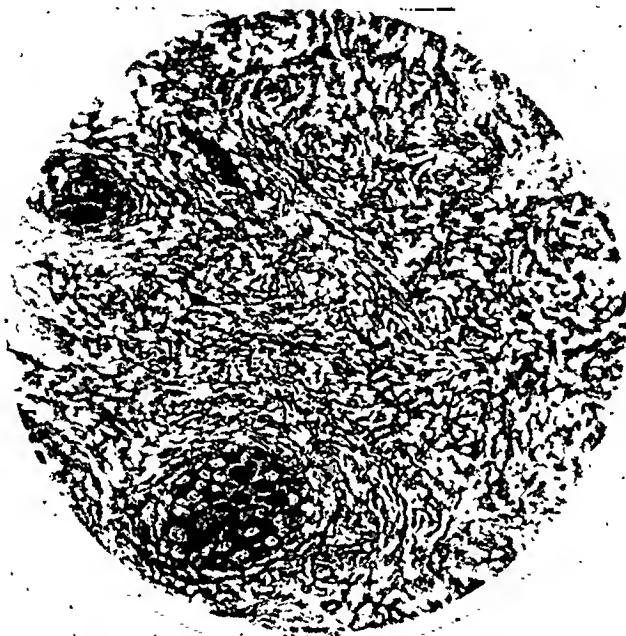


Fig. 2.—(Case 1.) Section of left gonad, ovarian stroma including epithelial cords with vacuolated cells. ($\times 200$.)

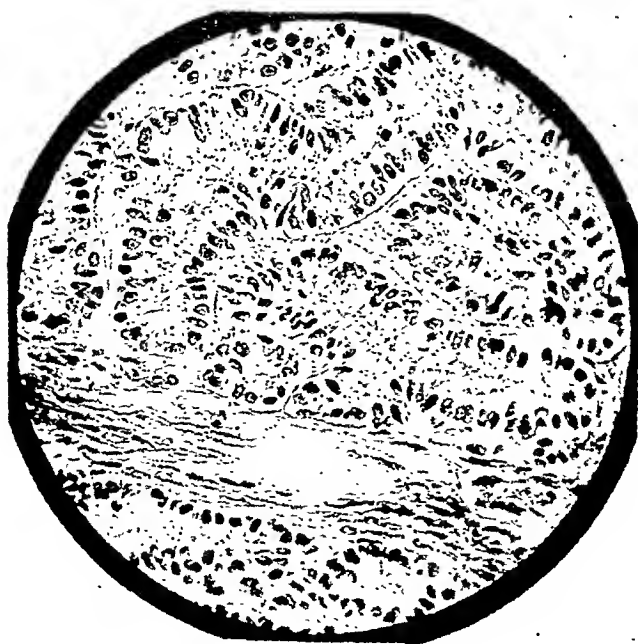


Fig. 3.—(Case 1.) Left gonad, tumor tissue. ($\times 260$.)

The medullary cords, i.e., the residues of the primary germinal cords, may further develop and form testicular tubules and various kinds of arrhenoblastoma.

According to Moszkowicz,⁶ the causes of this change from female to male and the growth of a tumor on the male portion of the gonad can be satisfactorily explained by Goldschmidt's intersexuality theory. All the cells of the organism are bisexual and contain male and female hereditary factors ($MMFF = \text{♀}$, $MMF = \text{♂}$). It depends only on the valence of the male and female hereditary factors, whether the individual's appearance is male or female. The greater the epistasy* is, i.e., the preponderance of one type of sex determining factors over the other, the better and more marked are the characteristics of that sex and the stronger will be its resistance to all opposing tendencies.

If the epistasy is low, the first dominating sex type gradually is exhausted and at a certain moment, the "turning point," the previously suppressed sex gains predominance. The lower the epistasy is, the earlier and the more thorough is the sex inversion. If it is very early and very thorough, a genetically female individual may develop a perfect male appearance and vice versa. If the sex reversal occurs at a later stage it can transform only that part which has not yet been definitely determined. An individual whose development has started as one sex, but from a certain moment, the turning point, changes to the opposite sex, is intersexual according to Goldschmidt.²

There is also no doubt that the two reported cases are intersexes with the turning point occurring in the stage when the somatic characters were already definitely sex-determined, while the stage of development of the gonads still allowed them a change from female to male.

Summary

1. Two cases of benign testicular tubular adenoma in two sisters are reported. The gonads consisted preponderantly of testicular tissue; the ovarian tissue was represented only by islands of ovarian stroma. In spite of the predominantly male character of the gonads, the patients looked and felt perfectly feminine. Each sister had female external genitals, a vagina, but no or almost no uterus and only a tiny tubal rudiment.
2. The removal of the malformed gonads caused severe deficiency symptoms.
3. The genealogic tree of these sisters showed that several members had abnormalities of their sexual organs and their sexual personality which marked them as intersexual individuals.
4. The gonads of these cases are interpreted as ovotestes. Embryologic facts as well as Goldschmidt's intersexuality theory are applied to explain the origin of this malformation.

*In Mendelian heredity the hiding of one character by another superimposed upon it, the two not being allelomorphs (Stedman).

assume that the effect of gonadic deficiency depends primarily on the specific reactivity of the female organism.

The testicular tubular adenoma is a very rare tumor. It is impossible to evaluate the exact number of such cases since description and illustration in some case reports do not allow a strict differentiation from other closely related tumors. The occurrence of a testicular tubular adenoma in two sisters is unique.

The testicular tubular adenoma represents the most differentiated and most typical form of a group of neoplasms, which, according to R. Meyer, are derived from a male anlage and therefore are called arrhenoblastomas. Its resemblance to normal testicular tissue is evident. Notwithstanding that fact, such adenomas masculinize their hosts only in exceptional cases. As a rule, the more atypical the structure of the arrhenoblastoma the more masculinizing is its effect. A priori, one would expect the contrary. Heretofore, all efforts to explain this puzzle have failed.

To understand the origin of testicular adenomas a short embryologic review of gonadal development is necessary. In the first stages of development, the gonads of both sexes have the same structure. In embryos of 9 mm. length, radiating cords of epithelioid cells suddenly occur below the germinal epithelium of the genital fold, forming the so-called primary germinal cords. At a later stage, secondary germinal cords appear under the germinal epithelium, pushing the primary cords deeper toward the center of the gonad (Gruenwald³ and others). There the primary cords join an epithelial network, the so-called rete, which also originates within the gonadal blastoma and which, by means of the urogenital junction, meets the neighboring tubules of the primitive kidney, the Wolffian body.

Qualitative and quantitative changes of the primary and secondary germinal cords mark the sex of the gonad. Generally one can say that in the testicle the primary and in the ovary the secondary cords predominate in quantity and importance. In the male gonad all the single constituents of the indifferent gonad grow and develop in the direction of the original architectural plan. The prevailing part of the seminiferous canaliculi originates from the primary germinal cords. In contrast, in the female gonad only the secondary germinal cords build up the essential ovarian tissue. The primary germinal cords, the rete and the urogenital junction regress under normal conditions, forming only insignificant rudiments in the ovarian hilum.

These rudiments represent the potential male part of the ovary. From the embryologic standpoint every ovary represents an incomplete ovotestis or, stressing the sterility of the central male part, a testoid, according to A. Kohn.⁵ Under pathologic conditions the male rudiments may awake to new life and give origin to tumors with male character.

of the clitoris, abnormalities of the breast, or other external male characteristics. The character of the voice was female. Blood pressure was 170/110.

On April 17, under gas-oxygen-ether anesthesia an operation was performed in which both tubes and ovaries were removed. In place of the left ovary an immense multilocular cystic tumor was found filling the entire pelvic and abdominal cavities. The right ovary lay prolapsed in the cul-de-sac, buried by adhesions. Following the operation there was complete abolition of headache. There was no other immediate change. Following discharge from the hospital, the patient was seen in November, 1940. She was still obese. Hirsutism was still present and as far as could be seen appeared no different than previous to operation; this, despite the fact that the patient claimed she shaved only twice a week. In January, 1941, hypertension was found to persist, being 180/110. There was no loss of weight. Aug. 11, 1942, her weight was 253 pounds, blood pressure 160/110. There was no recurrence of headaches. The only other striking change was in her demeanor. She was cheerful and had no complaints while previous to operation she had had suicidal intents.



Fig. 1.—Hematoxylin and eosin section showing islands of (ovary of Case 1) clear cells surrounded by stroma cells.

Gross Pathologic Findings.—The specimen consisted of a large ovarian cyst with an attached Fallopian tube and a smaller solid ovary with attached tube. Both tubes except for distortion were essentially normal. The right ovary was elastic in consistency, enlarged, weighing 21 Gm. and measuring 5 by $3\frac{1}{2}$ by $2\frac{1}{2}$ cm. The outer surface contained thin fibrous adhesions. On section the ovary was solid, being composed in the main of gray colored tissue intermingled with areas light yellow in color. Numerous small cysts were present close to the surface. The ovarian cyst was large, multilocular, partially collapsed and, though much of its content had been lost, weighed 780 Gm. The walls of the various cysts were thin with smooth inner surfaces. The contained fluid was thin and straw colored. Nowhere was the tumor solid. The smallest locule measured $2\frac{1}{2}$ cm. in diameter.

Microscopic Findings.—The ovarian cyst appeared to be of the pseudomucinous type with here and there small nests of clear polyhedral cells similar to those found in the Brenner tumor. The right ovary was composed chiefly of stroma cells, normal in size and appearance, ar-

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HYPERPLASIA AND LUTEINIZATION OF OVARIAN STROMA ASSOCIATED WITH MASCULINIZATION

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IT IS our purpose in this communication to present two case reports exhibiting obesity, hirsutism, and amenorrhea associated with unique ovarian alterations. One of these patients suffered also from hypertension. Both cases appear similar to those recently published by Geist and Gaines,¹ who apparently were the first to emphasize unusual changes observed in the ovaries. These consisted in enlargement of both ovaries, hyperplasia of stroma cells, the presence of nests of clear cells throughout the stroma, and hyperplasia and luteinization of the theca layer of atretic follicles. The authors generously credit Bergstrand² as describing in a case exhibiting Cushing's syndrome somewhat similar findings in an ovary. In reviewing this case for ourselves we noted that Bergstrand observed perifollicular luteinization, but did not mention diffuse hyperplasia of stroma cells. Masses of fat-staining cells are described but these he was unable to differentiate from atretic corpora lutea. In contrast, the islands of clear cells presented no such problem to the first two authors.

Case Reports

CASE 1.—The patient, M. M., a 38-year-old white woman, entered St. Vincent's Hospital April 15, 1940, complaining of severe headache, obesity, and hirsutism. The headache, which was the most disturbing symptom, was continuous and had been present for more than ten years. At the age of 20 her weight was 90 pounds, at 30, 155 pounds, and at 38, 257 pounds. Hirsutism had been present many years and required daily shaving and often twice a day. Although married twenty years she had never become pregnant. She menstruated three times in all her life, the last time in 1925. Off and on she received courses of thyroid, pituitary, and ovarian endocrine therapy without effect.

Physical examination disclosed an extremely obese white female, weighing 257 pounds. There was pronounced hirsutism of the face. There was no increase in hair elsewhere. There was no hypertrophy

of thick collars of swollen theca cells about follicles, indicating definite hyperplasia of this layer (Fig. 3). A moderate number of these cells were polyhedral and clear, not unlike in appearance those of the clear cell islands. No remnants of corpora lutea were found in the ovary despite the fact that it had been completely sectioned.

CASE 2.—R. M., 36-year-old female, was admitted to St. Vincent's Hospital Dec. 13, 1939, complaining of backache, menstrual irregularity, and hirsutism. She was gravid ii, para i. The second pregnancy was terminated by induced abortion. In 1933 she became conscious of thinning of the scalp hair. Concomitant with coarsening of the remaining body hairs, she developed facial hirsutism, progressing until 1937 when she resorted to daily shaving. The hair on the rest of her body also increased in amount. Shortly after this, the menstrual flow became scant. For about four years she had periods of amenorrhea, varying from two to twelve months. In 1938 she was given injections for the amenorrhea. Her periods became re-established for a short time. The last menstrual period was Nov. 20, 1938, lasting three days. Her period previous to this was October 7, lasting eight days and profuse. In the past year her breasts diminished in size. In 1935 her weight was 230 pounds. By means of thyroid extract she managed to reduce.

The patient was well developed and moderately obese. The hair covering her head was thick and coarse. The face was covered with a heavy growth distributed about the chin and upper lip. The neck was short and thick. Both breasts were pendulous. The lungs and heart appeared normal. Blood pressure was 110/64. There was moderate obesity of the chest and abdomen. A few striae gravidarum were present. There were no palpable abdominal masses. There was diffuse hair distribution on the extensor aspect of both upper and lower extremities. Pelvic examination revealed a normal-sized ovary and normal uterus. Both ovaries appeared enlarged.

Laboratory Data.—Urinalysis was negative. Glucose tolerance test: fasting, 79; half hour, 177; one hour, 200; 2 hours, 125; 3 hours, 76; 4 hours, 62 mg. per cent. White blood count was 9,840; 82 per cent polymorphonuclear leucocytes; 1 eosinophile; 13 lymphocytes; and 4 monocytes. The blood Kahn was negative; nonprotein nitrogen, 25 mg. per cent; and the basal metabolism, plus 3. Aerogram of the adrenal areas was negative. X-ray of the sella turcica revealed no abnormalities.

Operative Findings, Dec. 30, 1938.—The uterus was normal. Both tubes and ovaries were prolapsed and densely adherent. The ovaries were large, white, hard, resilient and completely covered by adhesions. Except for adhesions the tubes were normal. The operation consisted of bilateral salpingectomy and oophorectomy. The endometrium was everted. It was noted that the patient was bleeding and that this had started the day before.

Following the operation, the patient noted that the hair of the scalp stopped falling out. She also believed that her facial hair grew more slowly so that she did not shave for a week.

The patient has been followed for four years. Her hirsutism persists although she still feels that the rate of growth has been slowed up so that she does not have a shave as often as she did before the operation. She remains moderately obese. Her chief complaint is backache and leucorrhea which she had previous to her operation. She has been attending the out-patient department constantly. Aerograms were re-

ranged in interlacing bundles and whorls. Scattered throughout the stroma were many nests of clear cells (Fig. 1), from 3 to as many as 50 to a cluster. The cells were moderately large, having a thin faintly staining boundary. Cytoplasm was scant and composed of a few fine granules. Its content consisted largely of lipoid material staining

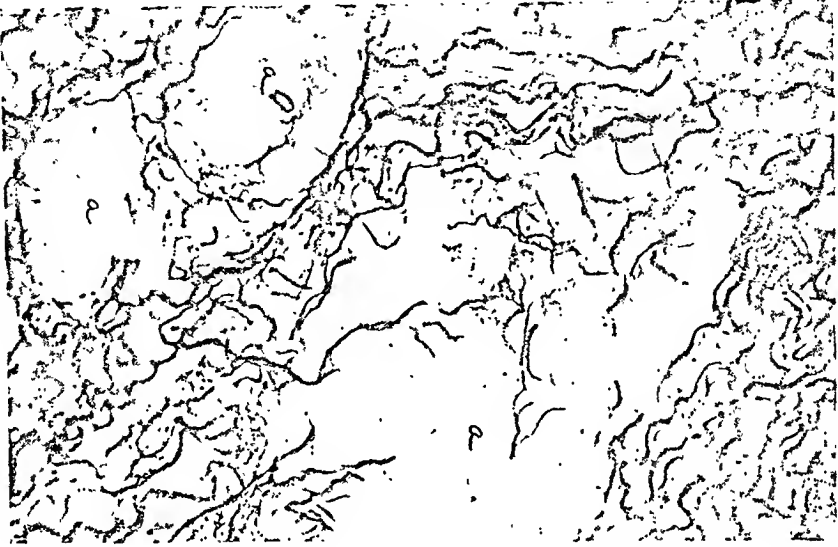


Fig. 2.—Reticulum stain, note reticulum surrounding islands (ovary of Case 1) of clear cells (*a*). Elsewhere the reticulum fibers envelop individual stroma cells.



Fig. 3.—Hematoxylin and eosin section. Photomicrograph of (ovary of Case 1) the layers of a Graafian follicle, (*a*) granulosa cells, (*b*) luteinized theca cells, (*c*) swollen hyperplastic theca cells.

deeply with sudan III. Reticulum fibers were abundant throughout the ovary. Where clear cells were present, it was evident that the fibers surrounded them as a group and not individually (Fig. 2). Graafian follicles were present in abundance. In general they were small in size. In some the various layers were atrophied while in others there was hyperplasia. The most conspicuous change consisted in the presence

Microscopic Findings.—Both ovaries presented a similar appearance. Their enlargement was due to diffuse hyperplasia of stroma cells. After considerable search, several small nests of clear cells similar to those of Case 1 were found (Fig. 4). Graafian follicles were numerous and most of them atretic. A few exhibited definite, pronounced hyperplasia of theca cells (Fig. 5). Some of these cells were enlarged, polyhedral, and clear. Reticulum was abundant throughout the ovary. Sudan III revealed a small amount of extracellular, finely granular, sudanophilic material.

Comment

Our cases are similar to those reported by Geist and Gaines, displaying obesity, hirsutism, and amenorrhea. One had hypertension. The removal of the ovaries produced no striking changes. Though both patients thought they shaved less often, the hirsutism persists. It should be mentioned that in Case 1 there was an immediate and complete disappearance of the primary complaint, namely, headache. The hypertensive state, however, remains. It is apparent, therefore, that the symptoms of masculinity and the state of hypertension cannot be ascribed to the ovary. The ovarian findings in both of our cases were identical, with the exception that in Case 2 nests of clear cells were very scant, and theca layer hyperplasia was observed in only a few follicles.

One cannot help but wonder as to the causation of the stroma cell hyperplasia, the theca cell proliferation and the identity, origin, and life cycle of the clear cell islands. Do the latter arise from stroma cells, does the presence of fat represent luteinization, or is it a regressive phenomenon, a form of fatty degeneration? We certainly do not have the answer. When Case 2 first came to our attention, its classification presented a perplexing problem. Temporarily it was catalogued as bilateral fibroma of the ovary. Later, when we read Traut and Marchetti's³ study of granulosa and theca cell tumors, we attempted to fit our cases into their group of pure lipid-free thecoma. In due course of time, when the ovaries of Case 1 were submitted to us, the problem of classification was reawakened. We submitted slides of these to Traut.* From his study he came to the conclusion that it represented partial luteinization of a theca cell tumor. Schiller,* on the other hand, influenced by the masculinity of the patient, diagnosed the clear cells as inclusions of adrenal cortical cell origin. Novak* who was also kind enough to study a section from Case 1 pointed out the similarity in appearance between the clear cells of the theca zone of atretic follicles and those of the cell islands and suggested that they might be luteinized granulosa cells. Plaut* noted the striking resemblance of the "clear cell islands" to the "interstitial gland" observed in rabbits. In our own opinion the findings in these cases do not represent a tumor but are a proliferative phenomenon induced by an endocrinologic imbalance affecting among other organs the ovarian stroma, some of whose cells undergo further change as evidenced by the appearance of fat. Hyperplasia and luteinization of cells of the theca layer probably are manifestations of the same phenomenon modified somewhat by the proximity of these cells to the ovum.

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*Personal communication.

peated but revealed nothing unusual. In summary, about the only change that followed removal of the ovaries was that instead of shaving every day she now shaves twice a week.

Pathologic Report.—Examination of the endometrium revealed it to be in the menstruating state. The left ovary was large, measuring $7\frac{1}{2}$ by $3\frac{1}{2}$ by $2\frac{1}{2}$ cm. It was oval in shape and felt firm. The surface was smooth but nodular. On section, the ovary for the most part was solid

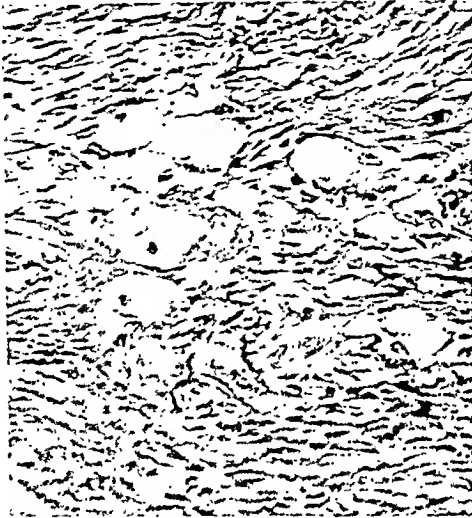


Fig. 4.—Islands of clear cells found in the ovarian stroma (ovary of Case 2).

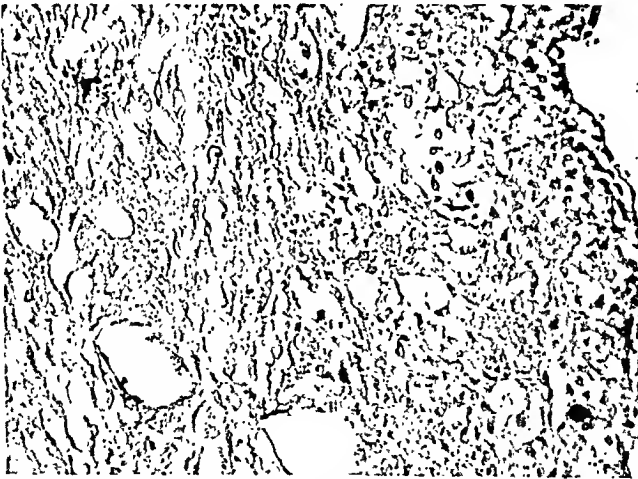


Fig. 5.—Photomicrograph of layers of a Graafian follicle (ovary of Case 2). Legends and changes same as Fig. 3.

and gray in color. Small cysts were present in the cortex. At the approximate junction of the cortex with the medulla, the tissue assumed a yellow orange color. Toward the center, the ovary was pearly gray and softer in consistency than the cortex. The right ovary was enlarged, weighing 35 Gm. and measuring 6 by $3\frac{1}{2}$ by 2 cm. Its surface was likewise nodular but smooth. The cortex was composed of solid, homogeneous tissue with a light yellow tint. Both Fallopian tubes appeared normal.

more severe cases, interruption of pregnancy was resorted to in addition to vitamin therapy. It is noteworthy that only few fatalities occurred in the cases reported by various authors during the last ten years (according to McGoogan only 7.5 per cent of those treated with vitamin B₁), although it must be taken into consideration that some of these cases were only mild.

There are only a few autopsy reports of cases of polyneuritis of pregnancy, and our knowledge of morphologic changes in the central and peripheral nervous system in particular is limited. Our observations on a case of polyneuritis of pregnancy, including a complete post-mortem examination, therefore, seemed justified.

Case Report

A primipara, aged 27 years, textile worker, had always enjoyed good health. Her past history, as given by the family, was essentially negative. There was no history of alcoholism, diabetes, or exposure to lead or other metals.

Two or three weeks after her last menses she developed severe nausea and vomiting and three weeks later was hospitalized in a near-by town. The nausea and vomiting persisted, but improved enough for patient to be discharged. However, it was necessary to re-hospitalize her for a period of ten days to two weeks on two or three occasions thereafter. She was treated symptomatically and with intravenous fluids. Approximately four to six weeks after the onset of nausea and vomiting she developed pain in the extremities, especially in the legs. Soon she had some limitation of motion of the arms and legs, and suffered great pain when touched. She was hospitalized for this condition, and treated for a period of one week with daily intramuscular injections of 2,000 international units of thiamin chloride. After two weeks she was discharged "greatly improved, but not entirely free from pain." Thereafter, she remained at home in bed, suffering severe pain in the extremities, was unable to use the extremities properly, and was extremely confused mentally. She suffered from headaches and blurring of vision. Moderate swelling of the ankles persisted. During the month prior to her last hospitalization she did not vomit, and managed to eat fairly well, although she was unable to use her hands to feed herself. Her home physician had given her considerable sedation, both by mouth and hypodermically, and while under the influence of these drugs she was comparatively quiet. More recently she experienced some vesical and rectal incontinence.

When I first saw the patient on Aug. 9, 1941, in the Charlotte Memorial Hospital, physical examination revealed the following findings: The patient was of medium build, well developed, appeared semistuporous and mentally confused. There was little evidence of dehydration; her temperature was 99.3° F. The head and eyes were grossly negative, and the ophthalmoscopic examination revealed normal fundi. The teeth were in fair condition. The thyroid appeared normal. The chest was entirely negative except for a moderate tachycardia. The systolic blood pressure was 120 mm. of mercury and the diastolic 80 mm. On abdominal examination, the uterus was felt just below the umbilicus. The fetal heart sounds could not be heard, and no fetal movements were perceived. Vaginal examination revealed a uterus enlarged to the size of a four or four and one-half months' pregnancy.

POLYNEURITIS OF PREGNANCY

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OBSTETRIC textbooks and literature contain very little about polyneuritis of pregnancy. However it is now recognized that the polyneuritis which may accompany or follow hyperemesis gravidarum is a dietary deficiency disorder, secondary to the vomiting and due to hypovitaminosis (vitamin B₁). According to Peters¹ in B₁ deficiency there is a defect in the oxidation of the carbohydrate intermediate substance in nerve tissue, particularly pyruvic acid. B₁ is the catalytic agent which completes this oxidation and the removal of the pyruvic acid.

Strauss² states that alcoholic polyneuritis, the toxic polyneuritis of pregnancy, diabetic, biliary, and gastrogenous polyneuritides, post-infectious polyneuritis, the Korsakoff syndrome and other similarly misleading names have concealed the true diagnosis of vitamin B₁ deficiency. He believes that these polyneuritides are clinically and pathologically identical with beriberi, differing only in the particular mechanism by which the deficiency is brought about. He states that the pregnant woman when nauseated often restricts her diet to concentrated carbohydrate foods low in vitamin B₁ content, and because of vomiting, fails to retain all that she ingests. Furthermore, her metabolism, and with it her vitamin B₁ requirement, is elevated during gestation, and it is possible that her powers of assimilation are reduced.

With the help of recently developed methods of determination of vitamin B₁ in the urine, it has been shown that there actually exists a marked vitamin B₁ deficiency in polyneuritis of pregnancy. Hildebrandt and Otto³ reported the complete absence of thiochrome in the urine in a case of severe polyneuritis of pregnancy. Vitamin B₁, however, could be demonstrated after large doses of injected vitamin B₁ shortly before and after delivery. Stähler⁴ comes to the same conclusion in his study on healthy pregnant women and those afflicted with polyneuritis of pregnancy. He found a deficit of 36 mg. in one such case.

Iswariah and Kutumbiah,⁵ in 1934, stated that in India peripheral neuritis was common during the puerperium in endemic areas of beriberi. These cases differed, however, in their clinical picture from those of true beriberi. An endocrine imbalance was suggested as a precipitating factor.

Berkwitz and Lufkin,⁶ in 1932, collected over 500 cases of polyneuritis of pregnancy dating as far back as 1854, but of these only 52 cases were undoubted, four of which were personal observations reported in detail. Plass and Mengert,⁷ in 1933, gave a critical review of 28 accepted cases of polyneuritis of pregnancy, adding 12 cases of their own to 16 cases previously reported. Since 1933 a number of other cases have been reported. Lubin and Newman⁸ reported a case of their own and mentioned cases reported by seven other authors since 1932. Among others, cases have also been reported by Luikart, Schaupp, Gerstle and Lucia,⁹ and most recently McGoogan¹⁰ reported a series of 15 cases.

From a study of the literature it is concluded that the milder cases were carried to term successfully by the use of vitamin therapy. In the

Considerable operative difficulty was encountered, due to a high rigid cervix and the nonelasticity of the tissues and supporting structures. Nevertheless, the patient stood the procedure well. Bleeding was minimal, and the patient returned to her room in fairly good condition. However, within a few hours it was evident that the patient was not doing well. The temperature had risen to 104° F., pulse rate 140, and respirations 34 per minute. She became very noisy and completely irrational. Sedation in extremely large doses was necessary. Twenty-four hours after the operation the temperature was normal, but during the day spiked to 104.2° F., and during the next three days it ranged from 101° to 104° F. Blood transfusion was repeated. Glucose and saline were given intravenously and by hypodermoclysis. The patient developed great difficulty in swallowing. Blood culture was negative. Six grams of sodium sulfapyradine were given intravenously. Finally death occurred on the fourth postoperative day, being preceded by a terminal pulmonary edema.

The necropsy, performed by Dr. Paul Kimmelstiel, revealed the following findings:

Anatomic Impression: Status postabortum. No gross pathologic findings.

Histologic Examination.—(Significant findings only.) *Heart:* Five sections through different portions of the heart muscle failed to reveal evidence of histopathologic changes. It was noteworthy that there was no "hydropic degeneration" of the heart muscle as described in beriberi hearts. *Lungs:* There were minute areas of aspiration and bronchopneumonia.

Adrenals: There were several foci in the zona fasciculata in which adrenal epithelial cells showed degenerative changes to the point of actual necrosis, granulation and disintegration of their cytoplasm. The areas were characterized by a rather massive infiltration with polymorphonuclear leucocytes. *Kidneys:* There was some acute dilatation of the tubules and very slight interstitial edema with round cell infiltration.

Uterus: The endometrium contained placenta and decidual tissue. Chorionic elements were seen to penetrate into the superficial layer of the muscularis. The inner surface was covered with fibrin and blood. Otherwise the organ was negative.

Sciatic Nerve: Myelin sheath stain revealed several areas in which the nerve fibers were disintegrated, having lost their myelin sheath, were blown up balloon-like. Fat stains showed in some areas the presence of numerous fat containing macrophages in between the nerve fibers.

Brain: A number of blocks were fixed in alcohol, embedded in celloidin, and stained by the Nissl method. A careful search was made for degenerative changes in ganglion cells. The following blocks were taken: three different portions from the cortex, three different levels of the basal ganglia, one section through pons, medulla oblongata, cerebellum, and three different levels of the spinal cord. The ganglion cells were clearly stained, but no change in the tigroid substance of any other pathologic change was seen in the ganglion cells, glia, or mesoderm. Spielmeyer stains on sections taken from three different levels of the spinal cord failed to reveal evidence of degeneration of the myelin sheaths.

Histologic Interpretation.—From histopathologic point of view only two positive findings of significance can be stated.

1. Degenerative changes in the peripheral nerves (sciatic nerve).
2. Recent cortical necrosis in the adrenal with polymorphonuclear leucocytic infiltration.

Examination of the extremities revealed limited mobility of all four extremities, and inability to lift the arms to a vertical position. There was no swelling of the joints, but there was considerable tenderness and hyperesthesia over the joints and all parts of the extremities. A diagnosis of polyneuritis of pregnancy was made.

After a neurologic examination was made, Dr. T. W. Baker reported the following: "There is no evidence of any cranial nerve paralysis. There is a marked weakness of all the extremities which seems symmetrical and equal. The patient is barely able to move the toes, but some quadriceps and psoas power in both legs is preserved. There is very little use of hands and fingers, and the hand grip is nearly absent. There seems to be fair use of the proximal muscles of the shoulder girdle. Exquisite tenderness of the calves to pressure is elicited. The reflexes of the lower extremities are entirely absent except for a slight flicker of the left Achilles reflex. The reflexes of the upper extremities are fairly normal and equal. The Babinski phenomenon is absent. There is undoubtedly some sensory loss in the feet, legs, and hands, but the extent is impossible to determine with the confused and uncooperative mental state of the patient." It was his opinion that the patient was probably suffering from polyneuritis of pregnancy, following hyperemesis gravidarum.

The laboratory findings on admission were as follows: Urine: Specific gravity, 1.012; reaction, alkaline; albumin, one-plus; sugar, negative; microscopic, few white blood cells and epithelial cells. (Catheterized specimen.) Blood counts: Hemoglobin, 62 per cent; red blood cells, 3,550,000; white blood cells, 8,700; differential: 69 per cent polymorphonuclears, 10 per cent stabs, 15 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophiles. Serology: Kahn, negative. Blood chemistry: nonprotein nitrogen, 32.9 mg. per cent; cholesterol, 235 mg. per cent; total protein, 7.2 Gm. per cent; icterus index, 4. Gastric analysis: Normal amount of free hydrochloric acid present, using histamine as a stimulus. Spinal fluid: Normal pressure (125 mm.); color, clear; total protein: 62.5 mg. per cent; globulin, normal; cell count, one lymphocyte present; Kahn and colloidal gold, negative. Cervical smear revealed many gram-positive bacilli, many epithelial cells, and a few pus cells. Culture: revealed lactobacilli. The electrocardiogram revealed only tachycardia.

Treatment during the next ten days consisted of vitamin B₁ (thiamin chloride), 200 to 250 mg. intramuscularly or intravenously daily, plus polyvitamins (especially riboflavine, 10 mg. daily, and nicotinic acid, 200 mg. daily) by mouth, iron (ferrous sulfate) by mouth, and liver injections daily. A diet of lean meats, vegetables, fruits, and milk was forced. It was necessary to resort to frequent sedation to keep the patient quiet. She was mentally confused and irrational most of the time, and would cry or scream throughout the night. During the ten-day period of observation, the strength of the extremities definitely improved, but there was no change in her general condition. Involuntary stools and voiding were almost constant. A low grade temperature was constantly present.

In view of the symptoms, interruption of pregnancy was believed to be indicated, although it was doubtful that it would alter the course of the disease at this stage.

Following preparatory blood transfusion, pregnancy was interrupted by a vaginal hysterotomy, performed under cyclopropane anesthesia.

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LEFT-SIDED PELVIC LESIONS SUBSEQUENT TO APPENDICITIS

Report of Three Cases

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APPENDICITIS in some of its protean manifestations frequently interests the gynecologist. Problems in differential diagnosis between appendicitis and primary salpingitis, tubal pregnancy, renal colic, etc., occasionally arise. During the course of severe appendicitis in women, the cul-de-sac of Douglas may be the site of abscess formation either before or after the removal of the appendix. Appendicitis as a source of infection causing tubal closure and sterility is probably common. Severe damage to the right adnexal structures from inflammations primary in the appendix is well known.

Less frequently reported, because less common, is left-sided abdominal and pelvic infection during or subsequent to inflammations of the appendix. Nather¹ reports 9 such left-sided abdominal abscesses occurring during the course of appendicitis. He emphasizes the greater frequency of extension to the left side in children and points out the peculiar anterior position against the abdominal wall of at least a portion of the left-sided abscess. The mechanism of formation of such abscesses is reviewed. The most tenable idea seems to be that from a medially placed inflamed appendix exudate is shunted to the left abdomen over the superior surface of the bladder.

The purpose of this paper is to report observations on three young women who were seen with lesions in the left pelvis not during acute appendicitis but four years, eight months, and twenty-four years, respectively, subsequent to their first attacks. The impression is not meant to be conveyed that the right adnexal structures escaped all damage, but certainly the major lesions outside the unrecognized appendicitis were in the left pelvis only, and in all three this was true from the time they were first seen. The third with appendicitis twenty years before as a child, probably had peritonitis and more than left-sided abscess formation at the time of her attack.

Report of Cases

CASE 1.—D. P., an Italian girl, aged 15 years, single, entered the hospital complaining of lower abdominal pain, nausea, and occasional

It is noteworthy that the myocardium fails to reveal vacuolization as described in beriberi. Also an exhaustive study of the central nervous system does not show degenerative changes as described in vitamin B₁ deficiency.

Comment

A case of polyneuritis of pregnancy in a late stage of the disease is reported in which death occurred notwithstanding treatment with massive doses of vitamin B₁ and interruption of the pregnancy.

It can hardly be denied that polyneuritis of pregnancy represents a manifestation of vitamin B₁ deficiency. Therapeutic results and biochemical determinations of thiochrom output in the urine constitute convincing evidence. The finding of degenerative changes in the peripheral nerves in our case confirms this assumption.

It may be noted, however, that the organic changes which are usually observed in similar cases of profound depletion of vitamin B₁ are absent. Although myocardial damage and degenerative changes in the central nervous system may be absent in vitamin B₁ deficiency, it is generally assumed that death in beriberi is due to cardiac damage and subsequent circulatory failure. Our patient showed no signs of this throughout her illness, nor was there evidence of circulatory impairment or vacuolization of myocardial muscle fibers at autopsy.

It is furthermore noteworthy that a careful study of the central nervous system failed to reveal evidence of degenerative changes, particularly in the spinal cord. The autopsy findings, therefore, though compatible with vitamin B₁ deficiency, are not characteristic of those cases in which death is due to beriberi. The rather extensive acute necroses in the adrenal cortex may be significant in regard to the mechanism of death, but since no mention of such changes is made in previous reports, no comment is made at this time.

Not much improvement could be expected from specific therapy in the advanced stage in which the patient came under our observation. Although actual degenerative changes in the spinal cord and ganglion cells are not observed, it must be assumed that in later phases of polyneuritis of pregnancy the peripheral neurodegeneration becomes practically irreversible in spite of massive and continuous doses of vitamin B₁. Others have pointed out that involuntary micturition and defecation must be taken as ominous signs, indicating that apparently the threshold of reparability has been passed. The experience in our case seems to confirm this observation.

In a case of this type when the physician apparently faces insurmountable difficulties he may, as we did, resort to interruption of pregnancy, although this procedure admittedly has no clearly defined specific rational indication other than the thought that a disease precipitated by pregnancy may be influenced by its interruption. It is, however, possible that this procedure may hasten the death of the patient as it probably did in our case. This experience seems to bear out McGoogan's conclusion that "therapeutic abortion is contraindicated in polyneuritis of pregnancy."

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At operation a large, flaccid, thin-walled adherent tuboovarian inflammatory cyst on the left was encountered with part of the cyst intraligamentary. The right tube and ovary were surrounded with fibrous adhesions, but the tube was patent. Upon investigation of the appendix, it was found that it had spontaneously amputated itself at some time in the patient's life. At the base there was a stub 1 cm. long completely sealed over except for a thin fibrous cord representing the remainder of the appendix. The region of the cecum was fairly free of adhesions. The cyst, made up of the left tube and ovary, was removed, and the residual of the appendix amputated inverting the stump as usual.

Upon study of the cyst the criteria for tuboovarian inflammatory cyst seemed to be fulfilled. The lumen of the dilated tube communicated with the cystic cavity and the only lining was a very flat serous epithelium. The tubal fimbriae could not be found flattened out inside the cyst.

After operation it was learned from the patient's sister that at the age of four years there was a serious illness diagnosed as appendicitis and peritonitis. The patient was never operated upon because it was thought she was too ill. After many weeks, recovery from the illness was apparently complete.

Recovery from the operation was uneventful.

Summary

Two cases of chronic left tuboovarian abscess and one case of left tuboovarian inflammatory cyst are reported long subsequent to primary attacks of appendicitis.

In young women appendicitis as a source of even left-sided pelvic lesions must be borne in mind.

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PROLAPSE OF THE FIMBRIATED END OF THE FALLOPIAN TUBE THROUGH OPERATIVE SCAR IN ANTERIOR VAGINAL WALL

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ON SEPT. 20, 1940, Mrs. C. R., a 41-year-old, syphilitic (Wassermann 2-plus), 98 pound, married female, gravida v, para v, was admitted to the surgical division of St. John's Hospital. Her chief complaint was pelvic discomfort of two years' duration.

The outstanding pathologic conditions found were as follows: marked pelvic floor relaxation due to old lacerations and multiple deliveries, with large cystocele and rectocele, first-degree prolapse of the uterus, a large, markedly lacerated cervix with endocervicitis, and a small umbilical hernia.

vomiting, for five days. For four years there had been attacks of right lower quadrant pain with nausea. On six occasions during the last ten months she had been seen in the out-patient department with lower abdominal pain and a diagnosis of salpingitis was made. Since the hymen was intact, and there were no stigmas of lower genital tract gonorrhea, the tubal lesions were thought to be tuberculous.

On admission, the white blood count was normal and there was no fever. The erythrocyte sedimentation rate was rapid. On rectal examination there was a mass in the left fornix 5 cm. in diameter, with slight induration to the right of the uterus.

At operation an abscess containing a few drams of pus was encountered in the left pelvis anteriorly. Both tubes were inflamed but patent. The operator still believing the infection to be an acute tuberculosis removed both tubes. After completing the pelvic operation, the cecum was delivered, and the appendix was found to be thick and indurated with a perforation in its middle third tightly walled off by omentum. It was removed.

Except for moderate infection of the incision the patient made a good recovery.

CASE 2.—J. H., a school girl, aged 15 years, entered the hospital complaining of attacks of vomiting and progressive weight loss for eight months. The patient was in school through this time, except on the average of every month to six weeks she was in the school infirmary for one or two days with vomiting and pain in the lower abdomen. The pain recently had become localized to the left lower abdomen. During these attacks she was seen by two or three different physicians and no definite diagnosis was ever established. After eight months, at the close of school, there was a weight loss of twenty-five pounds. At no time was she known to have fever or leucocytosis.

On admission, the leucocyte count was 9,100, and hemoglobin 67 per cent (Sahli). There was a slight tenderness over the lower abdomen with an ill-defined mass deep in the left pelvis above Poupart's ligament. The hymen was intact. On rectal examination, the mass in the left fornix was irregular, hard, firm, and measured 10 by 8 by 8 cm. There had been slight irregularity and some increase in menstrual flow. For this reason mainly, a diagnosis of a solid left ovarian tumor was made, having in mind granulosa cell tumor.

At operation a hard, indurated tuboovarian inflammatory mass with a small abscess anteriorly was encountered in the left pelvis. The right tube and ovary were mildly involved in fibrous adhesions. The appendix was found to be thick and indurated with a perforation in its middle third lightly sealed off by omentum. The left tube and ovary, being completely destroyed, were removed, and an appendectomy was done.

Recovery was uneventful except for moderate infection of the incision.

CASE 3.—G. B., a college student, 23 years of age, entered the hospital with no complaints. A few days previously on routine physical examination in the student health clinic she was told she had a large ovarian cyst. On examination, the abdomen was rounded below the umbilicus with a definite cystic tumor in that region. The hymen was intact. On rectal examination the rather flaccid cyst seemed to fill the left fornix, was partially fixed, and was assumed to be of left ovarian origin.

incision (Fig. 2, 4). A heavy purse-string suture was then placed around the closed incision, the vagina scarified (Fig. 2, 5) and the suture tied (Fig. 2, 6).

Histologic examination of the structure just below the mass showed typical Fallopian tube. The mass itself showed the fimbriated end of

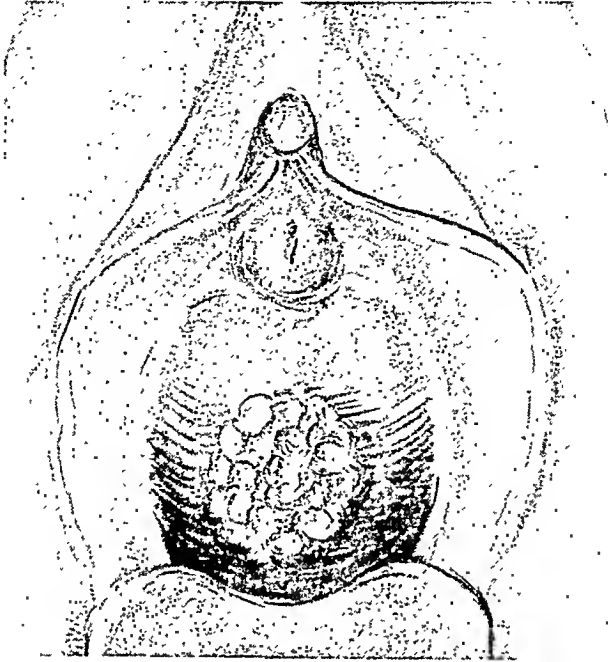


Fig. 1.

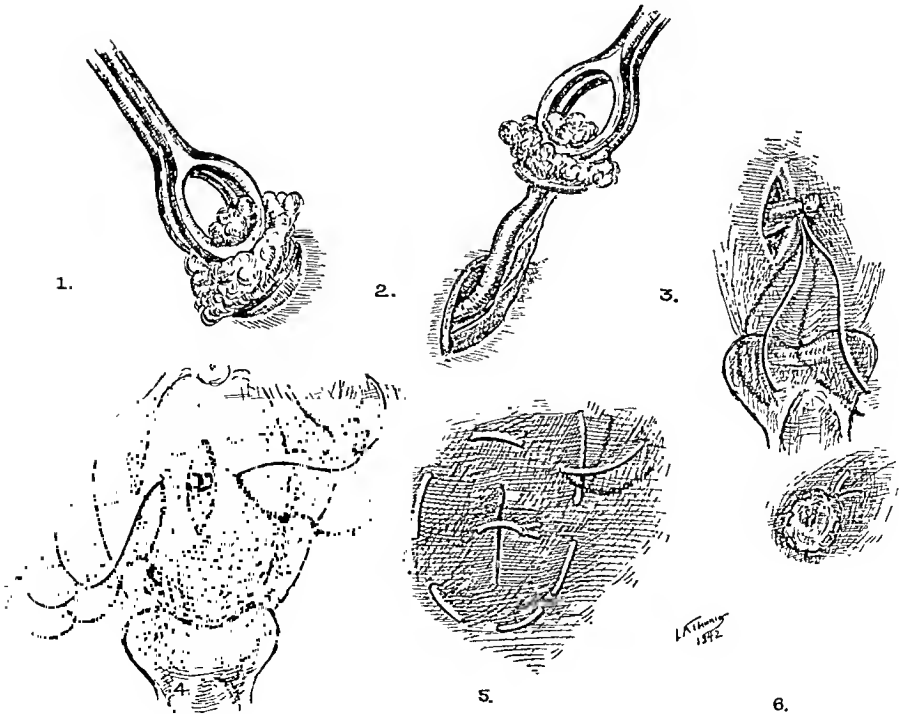


Fig. 2.

On Sept. 23, 1940, the following procedures were performed: (1) high amputation of the cervix, (2) anterior colporrhaphy with interposition of the uterine fundus, (3) sterilization by resection of the tubes at the cornual ends and burying cut ends between the folds of the broad ligament, (4) posterior colporrhaphy, and (5) plastic repair of the abdominal wall for the small umbilical hernia.

For the first four days postoperatively there was a moderately severe febrile reaction due to an infection in the right broad ligament, the induration being palpable along the course of the round ligament in the right inguinal canal. No evidence of any intraperitoneal infection was present at any time. From the second day on there was a bloody, purulent and foul vaginal discharge with a secondary hemorrhage estimated at about three ounces occurring on the seventh day postoperatively; a speculum examination failed to reveal the site of the bleeding or source of the vaginal discharge. The hemorrhage did not recur and by the fourteenth day postoperatively the vaginal discharge had ceased. The temperature subsided gradually as did the local and general systemic reaction from the fifth day onward and by the thirteenth day the temperature was normal and remained so. The patient was out of bed on the sixteenth day.

On Oct. 10, 1940, the seventeenth day postoperatively, examination revealed a clean, well-healed cervical stump, an apparently well-healed anterior vaginal wall, the interposed uterine fundus in excellent position, a firm well-healed pelvic floor with only a small superficial unhealed skin area in the perineum, and a well-healed abdominal wall with obliteration of the umbilical hernia. The patient was discharged from the hospital as cured on Oct. 15, 1940, twenty-two days postoperatively.

Early in January, 1941, the patient was seen in the out-patient department of the hospital. She was complaining of vaginal discharge. She was readmitted to my service on Jan. 8, 1941.

Findings on second admission: The blood Wassermann was now four-plus. On the anterior vaginal wall there was an elevated mass projecting about one-fourth of an inch above the surface. It was about $\frac{3}{4}$ to 1 inch in diameter and situated directly in the midline of the vagina about one-half inch above the urethral orifice in the site of the anterior colporrhaphy scar (Fig. 1). The interposed uterine fundus was palpable beneath the adjacent vaginal wall. The tumor was a dusky red in color, its base was sessile and firmly attached to the vaginal wall. The surface of the tumor was slightly irregular and nodular and bled on the slightest touch. The following opinions were expressed: (1) squamous cell carcinoma arising in an operative scar, (2) granuloma, possibly syphilitic, (3) endometrioma from endometrial transplant from cornua of uterus.

Biopsy was done on Jan. 13, 1941. The unexpected findings are shown in Fig. 2. The mass was held with sponge forceps and an elliptical incision made through the vaginal wall (Fig. 2, 1). With only slight traction on the mass, the Fallopian tube and a small amount of broad ligament were delivered (Fig. 2, 2). The tube and broad ligament were ligated about one-half inch from the point of vaginal exit (Fig. 2, 3); the ends of the suture were then used to bury the stump, fix it to the under surface of the vagina and close the small vaginal

a histologic description or microphotographs of these cases were not available for study. R. Schroeder (quoted by Kehrer¹⁰) resected a similar tumor, which recurred in the form of a squamous carcinoma.

In a symposium on malignant diseases at the Memorial Hospital, New York, Healy⁸ presented a case of benign epithelial papilloma of the vulva. The patient had suffered from pruritus vulvae for ten years. Treatment consisted of local excision of the bulky, papillary mass. No radiation therapy was given. The patient died five years later of a cerebral accident, and follow-up study during the five-year period revealed no recurrences.

Case Report

R. D. T., a 36-year-old, white, American, housewife, was admitted to the Beth Israel Hospital on Oct. 24, 1940, complaining of a "vaginal tumor" of four months' duration and pruritus vulvae of one year's duration.

Present Illness.—About one year ago the patient was hospitalized for pulmonary tuberculosis and shortly after developed pruritus vulvae. Upon discharge from the hospital six months later, she consulted a physician, who told her she had a "vaginal tumor." There has been no dyspareunia, vaginal discharge, or pain in the groins or thighs. The only complaint referable to the tumor was constant itching of the vulva, which was worse at night.

The family history was irrelevant.

Past History.—The patient had suffered with bronchial asthma for twenty-six years. She has had 8 attacks of pneumonia, the last attack occurring eight years ago. Tonsillectomy was performed at the age of 27 years. Menstruation began at the age of 14, recurred every twenty-six to twenty-eight days, and the duration of the flow averaged three and one-half days. Bleeding was moderate and not associated with pain. The last menstrual period occurred Oct. 30, 1940. During the period of hospitalization for tuberculosis, the patient had an amenorrhea of three months' duration. She had been married ten years, had never been pregnant, and had not resorted to contraceptives.

Physical Examination.—Except for an edentulous upper jaw, examination of the head and neck revealed nothing of note. Various pitched squeaks and râles were audible over the entire chest, and the breath sounds at the right base had a bronchoamphoric quality. The heart was not remarkable. The blood pressure was 118 mm. systolic and 64 mm. diastolic. No abdominal masses were palpable. There was no inguinal adenopathy. The fingers were clubbed.

The upper two-thirds of the right labium minus, part of the clitoris, and the upper end of the left labium minus were replaced by an ovoid mass (Fig. 1), which measured $3\frac{1}{2}$ cm. in its long axis and 2 cm. in thickness. The surface of the tumor was irregular and consisted of small papillary masses. It was not tender and did not bleed upon manipulation. Examination of the internal genitals revealed nothing of note.

Urinalysis revealed a trace of albumin. The Wassermann reaction was negative.

Treatment.—On Oct. 25, 1940, the involved area was excised under local anesthesia and the skin closed without drainage. The patient was discharged from the hospital three days later.

tube markedly changed in its histology because of infection and granulation. The individual fimbriae were no longer discernible as such.

The postoperative course was uneventful and the patient was discharged Jan. 19, 1941, six days postoperatively.

Discussion

To judge solely from the number of cases reported in the literature, the condition is very rare. The author found only five case reports by four writers.¹⁻⁴ However, from Kennedy and Campbell's book one gets the impression that prolapse of the tube as a complication of vaginal hysterectomy, at least, is not at all uncommon.⁵

With one exception, every case reported or spoken of has followed vaginal hysterectomy, some of which were drained.^{1, 2} The exception followed a posterior colpotomy for ectopic in which unusual drainage was used.⁴ In the case just presented the operation was an interposition procedure with resection of the tubes at the uterine cornua, complicated by the development of a moderately severe infection.

Follow-up examination, Jan. 14, 1943, two years after the second operation, showed the abdominal wall, pelvis, and pelvic floor essentially the same as on Oct. 10, 1940, seventeen days after her first operation. The anterior vaginal wall is smooth without traces of her second operative scars.

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BENIGN PAPILLARY EPITHELIOMA OF THE VULVA

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THE benign papillary epithelioma of the vulva is an extremely rare tumor.

After a careful survey of the literature on benign and malignant epithelial tumors of the vulva, it was noted that comprehensive monographs on vulval disease^{9, 16} and skin tumors^{1, 6, 14, 17} do not include this tumor among the benign epithelial neoplasias affecting the vulva. Novak¹⁵ and MacCallum¹³ have called attention to the "rare true papilloma" of the vulva, but a histologic description and pathologic differential diagnosis were not submitted in their texts. In a recent publication Folsome⁵ also mentioned the true papilloma, but histologic details were omitted.

Kehrer¹⁰ has described 3 cases of benign papillary epithelial tumors of the vulva. He distinguished them sharply from condylomata acuminata and called them verrucous papillomata. Kehrer also cited 5 similar cases^{1-3, 7, 11} which he had encountered in the literature, but

Microscopic Examination.—Representative blocks of tissue were fixed in formalin and stained with hematoxylin-eosin, van Gieson, iron-hematoxylin, and Weigert's elastica stain.

The picture was that of a papillary epithelial overgrowth with extreme keratosis and parakeratosis (Fig. 2). In some areas the keratotic masses were about twice the thickness of the epithelium. There appeared to be no difference in the degree of keratosis between the papillae as compared with their tips. In some areas the keratosis was seen to involve

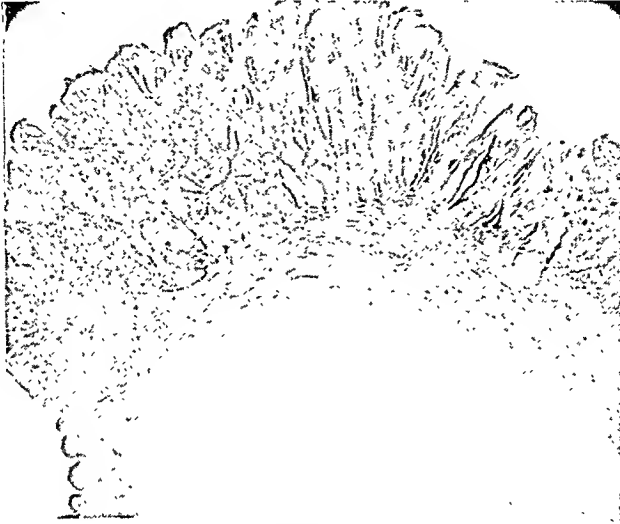


Fig. 2.—Paraffin section; hand lens magnification. The picture is that of a papillary epithelial overgrowth.

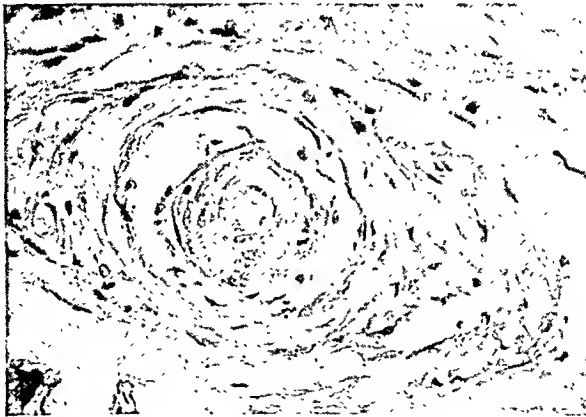


Fig. 3.—Sweat gland duct; its lumen is practically occluded by extensive keratinization.

the sweat gland ducts with apparent occlusion of their lumina (Fig. 3). In other areas the ducts appeared considerably distended. Throughout the papillary portion of the tumor the connective tissue cores were very thin; they contained many wide, thin-walled, mostly empty blood vessels. Occasionally they were hyalinized. The usual configuration of the squamous epithelium was maintained, and there were no abnormalities of cell structure or staining qualities. The intercellular bridges were distinct. The cells of the basal layer were arranged in an orderly manner

Subsequent Clinical Course.—The wound healed by primary intention and the pruritus subsided promptly. Periodic examinations revealed no recurrence or metastases. The patient has not lost weight and aside from asthma has been symptom-free.

Description of Specimen

Gross Appearance.—The specimen consisted of a piece of hairless skin, 5.5 cm. long, up to 1.8 cm. wide. A soft, ellipsoid mass, 3.5 cm. long and about 1.5 cm. high, protruded near its one edge. This mass was sharply demarcated from the skin, partly by a groove which in one place deepened into a pocket almost 1 cm. in depth. The surface of the mass

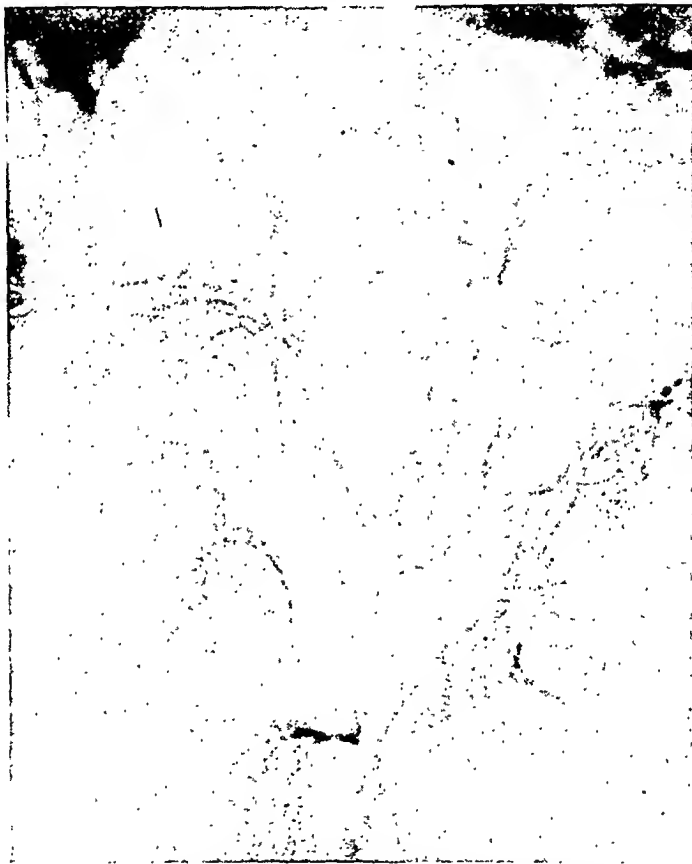


Fig. 1.—Tumor in situ. The ovoid mass is attached by a short pedicle to both labia minora and the clitoris.

was a shaggy whitish gray and consisted of many single finger-like formations packed closely together. The raw surface was formed partly by whitish gray tissue without markings and partly by fat tissue; this surface was concave, the deepest part of the concavity corresponding to the middle of the tumor.

Following fixation, the cut surface appeared as closely packed, finger-like protrusions. In its central portion the tumor had a thickness of 9 mm. The outline against the underlying tissue was straight in the thinner portion and slightly wavy in the thicker one. At one point the outline against the underlying tissue was slightly convex downwards and not entirely distinct.

Summary

A case of benign papillary epithelioma of the vulva is described and 4 similar authentic cases are collected from the literature. The tumor occurs as a single, round or ovoid mass, whose surface is papillary and nonulcerated. It is attached to the labia or mons veneris by a short pedicle or it may be sessile. It differs sharply from the condyloma acuminatum, with which it may be confused. The available evidence indicates that the tumor is anatomically and clinically benign.

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MALIGNANT LYMPHANGIOMA OF THE OVARY

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TRUE lymphangiomias of the ovary are very rare. To date there have been only four cases recorded: two by Kroemer,¹ one by Fleischer,² and one by Sidall and Clinton.³ To this we add one of our own, making the total number of recorded cases five in number. Two cases have been excluded because they arose from dermoid cysts (Schottlaender⁴ and Rössle,⁵).

It is our purpose here to report the fifth case of lymphangioma of the ovary, and as far as we know, the first case in which malignant changes were present. Only such data having direct bearing on the neoplasm has been considered.

and exhibited no evidence of anaplasia (Fig. 4). Although at a few points the basilar portion had a somewhat plexiform appearance, there was no true invasion of the cutis. At the junction between epidermis and cutis, there was considerable infiltration with mononuclear elements and some polymorphonuclear leucocytes. Sweat glands were numerous, and some of them were atrophic. Hair follicles were occasionally seen, but sebaceous glands were sparse.

Discussion

The presence on the labia or mons veneris of an ovoid tumor, whose surface is papillary and nonulcerated, and which is either sessile or attached by a short pedicle, should suggest the possibility of a benign epithelioma. Unlike the condyloma acuminatum, this tumor occurs as a single growth, reaches appreciable size, and according to Kehrer¹⁰ is not associated with a foul odor, as is commonly the case with the condylomata

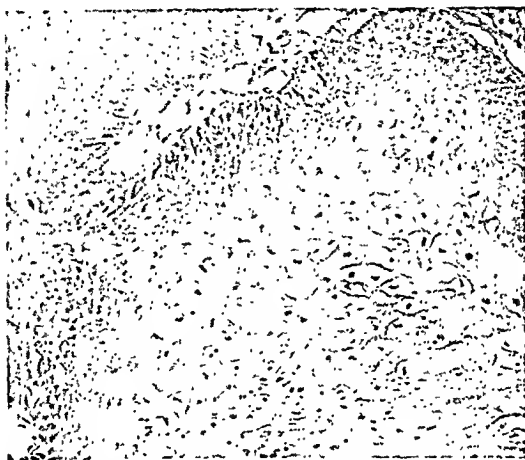


Fig. 4.—A typical portion of the tumor under medium magnification. Note the orderly arrangement of the prickles and basal cells. The connective tissue core is thin and contains numerous empty blood vessels.

acuminata. Histologically the benign epithelioma differs from the venereal wart by the presence of intense keratosis and parakeratosis, absence of edema of the epiderm, little, if any, stigmas of an inflammatory process, and a connective tissue stroma that is not congested.

There is no evidence to indicate that the neoplasm may recur following operative removal or that clinical malignant activity may be expected at some later date. In our tumor, Kehrer's series,¹⁰ and in Healy's case,⁸ there were no recurrences or subsequent clinical malignant manifestations. Schroeder's case recurred in the form of a squamous carcinoma. This case was quoted by Kehrer as a benign epithelial papilloma, but a histologic description of the tumor was never recorded in the literature.

Carcinoma-like condylomas of the penis have been described.^{12, 18} They have been regarded as benign neoplasias and were called condylomatoid precancerosis by Unna,¹⁸ who, too, regarded them as benign. These penile tumors were characterized by a downward infiltration of the epithelium, attributed to compression by a rapidly proliferating epithelium, and enlargement and differences in staining qualities of the epithelial cells. Such histologic characteristics are strikingly absent in the benign papillary epithelioma of the vulva.

Incomplete or poorly formed channels, in which endothelial proliferation had become so marked as to almost completely obscure the lymphatic spaces, was present. The endothelial cells varied in size and shape and contained hyperchromatic nuclei uniformly spherical or ovoid in shape. Masses of these cells extended into the surrounding tissue as buds. In most areas, extraluminal proliferation of endothelium was present and

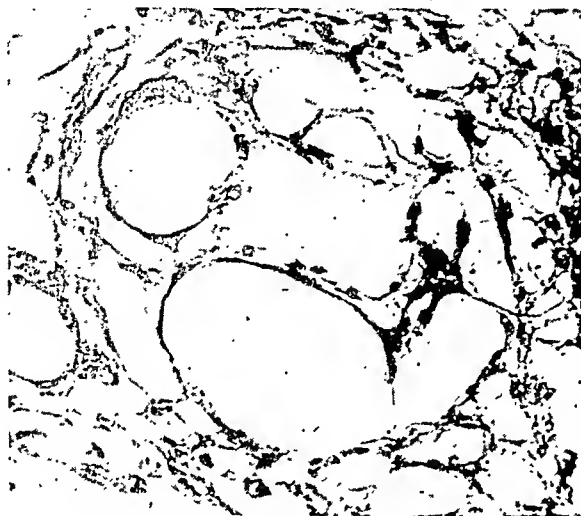


Fig. 1.—Section of the left ovary six months before death, showing closely packed regular lymphatic channels without extra- or intraluminal proliferation.

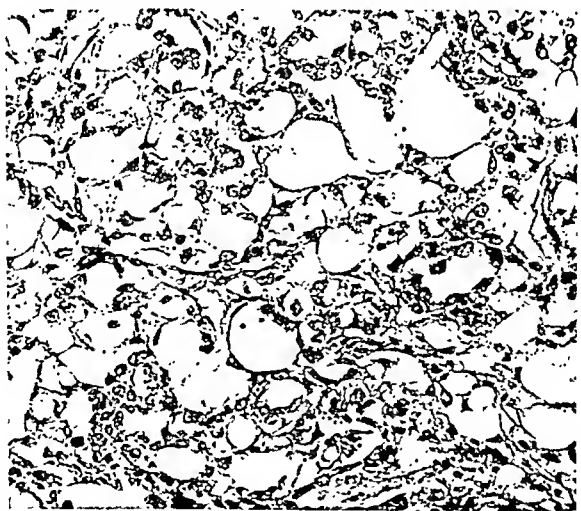


Fig. 2.—Section of the recurrent pelvic tumor mass at autopsy shows irregular lymphatic channels with extra and intraluminal proliferation.

occasionally formed solid sheets (Fig. 2). Large areas of necrosis and hemorrhage were also noted.

The right ovarian mass showed remnants of the normal ovarian stroma (Fig. 3) and neoplastic tissue similar to that described above.

The liver revealed numerous areas of necrosis with or without neoplastic cells. In many areas, there were well-constructed endothelial-

A colored female, aged 31 years, was admitted on Sept. 21, 1940, complaining of enlargement of the lower abdomen of one month's duration.

A palpable mass was present in the lower abdomen extending to the umbilicus. On Sept. 24, 1940, a large tumor was removed from the left adnexal region and a small portion of the right ovary was resected.

The left ovarian mass measured 15 by 12 by 7 cm. Its external surfaces were gray and smooth. Cut section revealed numerous cysts of varying sizes whose linings were pale brown and smooth and contained a yellowish translucent fluid. A microscopic diagnosis of benign lymphangioma of the left ovary was made (Fig. 1). Unfortunately the resected portion of the right ovary was lost.

The postoperative course of the patient was uneventful and the patient was discharged on Nov. 4, 1940.

On April 8, 1941, the patient was readmitted with abdominal rigidity, pain, swelling and a ballotable mass in the lower abdomen, the size of a four months' pregnancy.

A second laparotomy was performed on April 14, 1941, and revealed about 2,000 c.c. of serosanguineous fluid in the peritoneal cavity. Floating in this fluid were fragments of friable grayish brown neoplastic tissue. A tumor mass filled the pelvis and many other tumor masses were adherent to the small and large intestine, peritoneum, and the liver. The patient gradually became worse and died on April 22, 1941.

Autopsy showed all the abdominal viscera obscured by large masses of hemorrhagic grayish friable tissue which were attached to the peritoneum, liver, spleen, and intestine.

The pleural surfaces were smooth except for the diaphragmatic portions which were studded with tumor nodules up to 3 cm. in diameter. The spleen weighed 160 Gm., and tumor tissue was attached to its outer surface. Cut section revealed no evidence of metastasis. The liver weighed 1,430 Gm. Tumor nodules were present on its outer surface and cut section revealed many nodular areas up to 4 cm. The pancreas was embedded in a mass of tumor tissue. All the coils of the small intestine were surrounded by friable tumor tissue. A uterus, normal in size and shape, was present. Friable tumor tissue filled the cul-de-sac. On the left, the adnexal region was obscured by a tumor mass and the ovary was absent. The right ovary was replaced by a cystic mass 5 cm. in diameter with smooth external surfaces. Cut section revealed numerous cystlike cavities filled with a yellow translucent fluid similar to the left ovarian tumor which was removed surgically. Both tubes were embedded in the neoplastic tissue. The remainder of the organs showed nothing of note.

Microscopic Findings.—The left ovarian mass removed surgically on Oct. 24, 1940, consisted mainly of closely packed lymphatic vessels of varying sizes and shapes. These channels were lined by flattened, one-layered, endothelial cells having a fusiform nucleus (Fig. 1).

In a few small areas, however, the endothelium was several layers thick and consisted of intra- and extraluminal proliferations. Here, the endothelium was swollen and the nuclei more hyperchromatic. A large portion of the tumor mass had undergone necrosis and hemorrhage.

The second surgical specimen, as well as the autopsy material obtained six months later showed loss of the orderly arrangement of the lymphatic channels. All the sections taken through the neoplastic tissue were similar.

size and shape. A great deal of necrosis was present, apparently due to the rapid growth of the tumor which makes us believe that the tumor was malignant from the beginning. On pure morphologic grounds, it is difficult to call the first section malignant (Fig. 1). Serial sections were constant in appearance. It is possible that the malignant portions were destroyed by areas of necrosis. In the liver this seemed apparent as numerous large and small areas of necrosis were present with or without tumor cells.

In the post-mortem sections, a profound difference in the morphology was at once apparent. Varying and large amounts of extra- and intra-luminal proliferation had taken place. Instead of the flattened endothelium with its dark fusiform nuclei, the endothelium was more swollen and proliferative and the nuclei more vesicular. In some sections, intra-luminal budlike processes could be seen.

The question naturally arises because of the occasional presence of small budlike processes in the lumen that this might not represent tumors similar to those championed by Schiller⁶ as "mesonephroma ovarii." In our sections, unlike those of Schiller, the budlike processes represented localized proliferations of the endothelium and could in no sense be interpreted as mesonephric processes.

Recently Kazancigil, Laqueur and Ladewig⁷ have described three cases under the caption of papillo-endothelioma ovarii in which there were processes resembling glomerular-like structures. In addition angiomatous and diffuse endotheliomatous areas were apparent. Their first case also contained "granulosa" areas.

Summary

We have presented a case of an apparently morphologically benign lymphangioma of the ovary in which a resection was done. Six months later a local recurrence, peritoneal dissemination, and hepatic metastasis had taken place, and a new growth in the opposite ovary was present. A rather profound morphologic difference was evident between the primary and disseminated neoplasm, consisting of proliferation of the endothelium and changes in the individual cells. However, because of the marked necrosis of the primary together with marked hepatic necrosis present at autopsy make us feel that the tumor was malignant at its inception in spite of the regular benign morphology it presented.

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lined lymphatic channels with varying degrees of extraluminal proliferation. The adjacent liver cords were markedly compressed (Fig. 4).

The remainder of the organs showed no evidence of metastasis or any distinctive pathologic changes.



Fig. 3.—Section from the right ovary at autopsy showing normal ovarian stroma and neoplastic lymphangiomatous tissue.



Fig. 4.—Section taken through the liver revealing well-constructed endothelial lined lymphatic channels with varying degrees of endothelial proliferation. The hepatic cords are markedly compressed.

Comment

A diagnosis of a benign lymphangioma was made from the original biopsy, and six months later metastasis and dissemination had occurred. The purely morphologic diagnosis of malignancy in a lymphangioma is very difficult, even in the presence of varying degrees of extra- and intraluminal proliferation. This was practically absent in the first specimen and the tumor consisted of thin-walled dilated spaces, varying in

the forearm but could be extended. The fingers could not be fully extended. There were no external genitals. There was an imperforate anus. A small area on the posterior surface of the right hip suggested deviated position of the imperforate anus. The legs were completely fused, and there was a single foot with 6 toes, the foot extending to the left (Fig. 1).

Roentgen Ray Findings.—There were 13 ribs on the left side and 12 ribs on the right. The angle of the mandible on the right side was absent. The vertebral spine showed no well-defined arches; the impression was that of a complete spina bifida. The articular processes of the eighth and ninth thoracic vertebrae could be distinguished on the

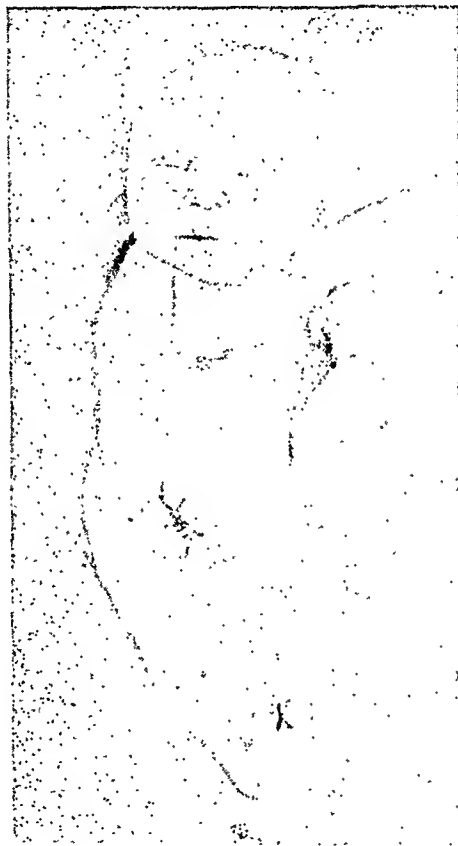


Fig. 1.—Note absence of genitals and fusion of lower extremities.

left side. The vertebral bodies were smallest in the region of the eighth and ninth thoracic vertebrae, and the largest in the region of the cervical and sacral vertebrae. There was a slight scoliosis to the left, and a distinct kyphosis in the area of the eighth and ninth thoracic vertebrae (Fig. 2). (Although there was the impression of a complete spina bifida there seemed to be present spinous processes in normal number.) The coccyx extended anterior to the femur. The pelvis appeared to consist of a right and a left os ilium, which were asymmetrical, and a heart-shaped bone between them. There was no proper hip joint but 2 femurs were somehow articulated on each side between the heart-shaped bone and the ilia (Fig. 3). The lower extremities showed a fusion. There were 2 femurs, 2 tibiae, and 1 fibula. The fibula seemed

NORMAL INFANT AND A SYMPUS MONSTER WITH A SHORT CORD IN A TWIN PREGNANCY

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(*From the Kings Daughters Hospital*)

THE most interesting features of the present case are: delivery of twins at term, a normal surviving infant and a sympos monster which died after five minutes; short umbilical cord of the monster, measuring only 5 cm. There were mono chorionic membranes, suggesting that the twins were of the single ovum type.

Mrs. J. J. L., white, aged 40 years, weight about 250 pounds, was first seen when admitted to the hospital, in labor, July 14, 1942.

First menstruation at 13, periods regular since. She has 8 living children, all boys, the second pregnancy being twins. There have been no miscarriages. Ages of her children are: 16, 14, 14, 12, 9, 6, 4, 2. All babies were large at birth. Patient stated that her grandfather was one of twins. Her last child was a breech presentation, and was delivered manually.

Last menstruation began Sept. 28, 1941; estimated date of confinement July 8, 1942.

Patient was obese and large framed. Head was normal, eyes clear, teeth good, breasts large, and heart normal. There was no history of any venereal disease. Wassermann was negative. Abdomen was very large, and abdominal muscles flabby. Patient was in the second stage of labor with the right foot presenting. Due to the extremely large size of the abdomen, a diagnosis of twins was made.

Because of the weak abdominal muscles it was thought wise to do a breech extraction. This was done under gas anesthesia and a large male child was delivered with no difficulty. The child was normal and respiration was immediate upon delivery. The placenta did not deliver at this time. Another fetus was felt in the uterus. Internal examination revealed a foot presenting but the other foot could not be felt. A manual delivery was also performed on this child. When the hips were delivered there was some difficulty in delivering the rest of the body. The child was eviscerated. The difficulty in delivering the baby was due to the shortness of the cord, the pull having torn away the umbilical area of the abdominal wall. The intestines were replaced and the wound sutured. The child breathed for about five minutes.

The placenta was delivered by the modified Credé method. Examination showed there was a single placenta with 2 amnions and 1 chorion. The cord of the first child was normal in length while that of the second child was only 5 cm. long. The placental areas of the normal baby and the monster were unequal, the proportion being about 2:1, respectively.

First child: A male which showed no abnormalities. Weight about 9 pounds. Second child: gross examination: The weight was about 4 pounds. The head showed an abnormality of the right lower jaw, the angle of the mandible being absent. The ears had a peculiar shape, were large and lay close to the head. The hands were flexed against

PREGNANCY AFTER TUBAL STERILIZATION

With the Report of Case Demonstrating Epithelium-Lined Connecting Tube

GEORGE L. CARRINGTON, A.M., M.D., BURLINGTON, N. C., AND
JAMES B. BULLITT, A.M., M.D., CHAPEL HILL, N. C.

THIS case is reported because it demonstrated the formation of a patent, epithelium-lined fibrous cord 20 mm. long that connected the separated ends of the divided oviduct after an attempted tubal sterilization. The operation was done in conjunction with a cesarean section and consisted of resection of a wedge from each uterine cornu and plication of a peritoneal fold as described in the case report. Pregnancy later occurred. Following the report the implications of the findings are briefly discussed.

Mrs. H. R. T., white, aged 30 years, two years previously when pregnant and near term, had been operated upon by one of us (G. L. C.) because of the dual indications of disproportion and mitral insufficiency of long standing nearing decompensation.

A low cervical cesarean section was done and a wedge resected from each uterine cornu, care being exercised to include the oviduct in the wedges. The walls of the V left by the removal of the wedges were sutured together, the tubes ligated, and the peritoneal fold from the tubes plicated over the raw area, separating the end of the tube from the cornual wound for a distance of about 2 cm. Number 2 chromic catgut was used.

When readmitted May 5, 1939, the patient was about three months pregnant. The mitral insufficiency was marked but compensated. She was operated upon (G. L. C.) on May 12, 1939, the supravaginal portion of the uterus with its contained pregnancy and both undisturbed, attached Fallopian tubes being removed. Her convalescence was uneventful.

Pathologic Report (S/39/1115) (J. B. B.):

"This specimen consists of a uterus, amputated apparently through the cervix. Its dimensions are: vertical 75 mm.; lateral 96 mm. (near fundus); anteroposterior 65 mm. The posterior surface is strongly convex, the anterior surface flattened (probably from lying on that surface during fixation). The left oviduct is represented by a flattened, irregularly crescentic mass, 20 by 14 mm., firmly plastered against the cornu by a peritoneal covering. When this is dissected free, no lumen can be found grossly or microscopically in the tube nor any opening into the uterus.

"The right oviduct is spirally coiled, forming about one and one-third turns, closely apposed to the uterine wall at the level of the cornu, and (except for about 15 mm. of the distal end) firmly bound to that wall by peritoneum. The fimbriae are shrunken to blunt stubs only one or two mm. in length. Seen through the peritoneal covering the proximal end seems squared off and is located about 20 mm. below the normal point of attachment. When this tube is dissected free and reflected

to be on the medial side of the left tibia. The soft parts allowed one to distinguish a separation between the femurs but not between the tibia. There was one foot, which projected at a right angle from the distal end of the left tibia. One tarsal bone, six metatarsals, and six phalanges were present.



Fig. 2.

Fig. 2.—The coccyx can be seen in front of the femurs. The spinous processes can be counted in this picture.



Fig. 3.

Fig. 3.—The heart-shaped bone and asymmetrical os ilia can be distinguished easily.

While in the literature there are many records of symphysio monsters, the present case is apparently unique in the occurrence of such a monster in a twin pregnancy of which only five instances have been reported.

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This portion of the lumen is somewhat dilated and a little placental tissue projects into it.

“When the uterus is split open laterally an apparently normal fetus (70 mm. long from occiput to coccyx) is seen. The placenta is attached posteriorly, the cord springing from a point about 15 mm. below and to the right of the center of the posterior wall.”



Fig. 3.—Section of channel through uterine wall which contains a mass of decidua cells. $\times 58$.



Fig. 4.—Decidua cells from Fig. 3. $\times 160$.

downward, a slender cord (20×2 mm.) is exposed to view. Attached at one end to the side of the proximal end of the oviduct, this cord runs upward to attach at its other end to the uterine wall at about the location of the normal isthmus. Microscopic sections, made at short intervals through the oviduct, show it patent throughout, with essentially



Fig. 1.—Section through remnant of oviduct. $\times 58$.



Fig. 2.—Section through canalized fibrous cord connecting this oviduct with the uterine cornu. $\times 58$.

normal architecture except for considerable simplification of the mucosal folds. Sections through the above mentioned connecting cord show it to be a fibrous tissue tube the lumen of which is lined by a thin mucosa, similar to that of the oviduct. Sections of the uterine wall show the continuance of the lumen of the cord to open into the uterine cavity.

4. Careful hemostasis should be observed, as blood clots delay scar tissue healing and give epithelium a chance.

5. Sterilization should preferably be performed on the nonpregnant uterus, because it is far less vascular than the pregnant uterus, and bleeding in the cornual resection is less likely to result in hematoma.

6. A dry technique, silk, cotton, fine linen, should be used on uterus, tubes, broad and round ligaments. The moist technique of catgut with the serum reaction about it over the time required for its absorption delays scar tissue healing and gives the epithelium of the tube a better chance over a longer period of time to form a canal.

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BRENNER TUMOR OF THE OVARY COMPLICATING PREGNANCY

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ORTHMANN,¹ in 1899, reported what was probably a Brenner tumor eight years before Brenner³ in 1907 reported his three cases. Brenner designated these tumors "oophoroma folliculare" and confused them with granulosa cell tumors. It was Robert Myer⁴ who, in 1932 described the characteristics of this tumor and offered the generally accepted histogenesis. It is usually agreed that these tumors have their origin from certain cell rests as originally described by Walthard² in 1903.

While Brenner tumors are not uncommon, only four have been reported occurring as a complication of pregnancy. Novak and Jones,⁶ in 1939, reported 122 cases, three of which were associated with pregnancy. In the first, the patient was four months pregnant when the tumor was removed; while in the second, pregnancy was noted only at the time of hysterectomy and bilateral salpingo-oophorectomy. In the third instance, pregnancy was diagnosed by finding decidual tissue in curettings. In 1940, Siegel⁷ reported a single case in which the tumor produced dystocia and was removed at the time of cesarean section. In Danforth's series,⁵ reported in 1942, pregnancy was not mentioned. The purpose of this report is to add a fifth instance of Brenner tumor complicating pregnancy.

Case Report

R. R., aged 32 years, para i, gravida ii, whose last menstrual period was May 22, 1942, began uterine bleeding on July 3, 1942. Immediate treatment was instituted, including ephynal acetate, 10 mg., and desiccated thyroid, one-half grain, three times daily, and 5 mg.

This specimen showed very well the urge of epithelium to reconnect. A rather cursory examination of the literature indicates that the process is frequently successful after attempted sterilizations and suggests that better-thought-out obstacles are necessary for its prevention. Operations on the flexible part of the oviduct appear to have about 5 per cent failures. Resections of the cornua appear much more certain of success.

We found references to three patients, however, in whom pregnancy occurred after removal of most of the uterus, and a fourth in whom it occurred after a bilateral salpingectomy accompanied by resection of a wedge from the uterus. Schultze³ observed pregnancy after total resection of both tubes and amputation of the fundus. Liepman^{1a} reported it after supravaginal hysterectomy. McMillan and Dunn^{1b} reported two pregnancies in the same patient after supravaginal hysterectomy with excision of all of one tube and ovary and part of the other tube. Lasch⁴ reported pregnancy in a woman who had both tubes, wedges from the uterine cornua, and one ovary removed.

An examination of the original operations in the above cases shows the possibilities for recanalization in two of them. In the case reported by McMillan and Dunn, the cut end of the remaining tube had been stitched in with the peritoneum over the stump of the cervix. Cervical canal and tube end may have been in apposition, a suture may have cut through the tube a few days after operation, or a small dead space may have invited epithelization. In the case by Lasch, the remaining ovary had been sutured against the uterine wall, apparently at the site of the removed wedge. A hematoma in the site from which the wedge had been removed would have furnished an excellent opportunity for the epithelium to finish the path from uterus to ovary.

Schultze³ reported a case that closely parallels ours. This woman had been supposedly sterilized by resection of the isthmic portions of the tubes. Conception took place about fifteen months after operation. On the left side continuity of the tube appeared to have been restored by a fistulous duct. Its epithelium was low, nonsecreting, without fimbriae and partly formed by cells of the decidual type. Musculature was not present. On the right side a fistulous duct was in the making. Both stumps terminated in it but had not yet joined.

The tendency of epithelium to connect with epithelium is well known. What might happen is illustrated in a patient fifty-five years of age upon whom one of us (G. L. C.) operated a few years ago. She might well have had an abdominal pregnancy after a total vaginal hysterectomy, if she had been younger. The wound healed with a small fistulous tract through the vaginal vault, the approximated pubocervical and uterosacral ligaments, broad and round ligaments, forming a patent canal from vagina to peritoneal cavity, that required six months of curetting and cauterizing to obliterate.

As we consider the problem of occluding the oviduct a few basic conclusions appear justified.

1. The ease and rapidity of an operation should seldom, if ever, be deciding factors in determining procedure.
2. The ends of the divided oviduct should have the maximum of spacial separation.
3. In that spacial separation, the greatest opportunity for scar tissue formation and peritonization should be afforded.

thesia. The abdomen was entered through a low midline incision. The right ovary was found to be replaced by a smooth, thin-walled, freely movable cyst, about 15 cm. in its greatest diameter, which displaced the uterus posteriorly. There was also a small thin-walled cyst of the left ovary 3 cm. in diameter. Both Fallopian tubes appeared normal. No corpus luteum was noted. The corpus uteri was soft, retroverted, and symmetrically enlarged, corresponding to the period of amenorrhea. No other pathology was found. A right salpingo-oophorectomy was then performed.

Pathologic Examination.—*Gross:* The specimen consisted of a right ovary which had been replaced by a large, thin-walled cyst measuring 15 cm. in greatest diameter. It was divided into two distinct sacs. Attached was the Fallopian tube, which was thin-walled and did not appear unusual.

Microscopic Examination.—(Dr. Herbert Traut, Cornell University School of Medicine.) Sections of the Fallopian tube showed a thin wall in which the vessels were injected, and there was an occasional small focus of lymphocytic infiltration. Sections of the ovarian cyst showed a thin fibrous wall in which were numerous islands of closely packed epithelioid cells, resembling the cells found in Brenner tumors. This was a benign growth which evidently had become cystic.

The pathologic diagnosis was cystic degeneration of a Brenner tumor, with chronic salpingitis.

The postoperative course was entirely uneventful. Preoperative therapy was resumed, the patient receiving desiccated thyroid, one-half grain, three times daily, ephedrine acetate, 3 mg., twice daily, and 5 mg. of proluton daily. The patient was discharged from the hospital on Sept. 7, 1942, and since that time the pregnancy has progressed normally.

Discussion

A complete survey of the literature on Brenner tumors reveals only four instances which have been associated with pregnancy. To these has been added a fifth case in which the tumor was discovered during pregnancy, and which was removed without disturbance of the normal course. The small cyst of the left ovary probably had its origin from the corpus luteum. The cessation of bleeding at approximately the end of the third month is accounted for by the hormonal action of the placenta, which begins its function at this time.

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of prandone daily. The bleeding was never profuse, but irregular "spotting" continued until Aug. 15, 1942.

Physical examination revealed a well-developed and well-nourished woman, 69.5 inches tall, and weighing 129.25 pounds. The eyes were normal, and the teeth in good condition. The thyroid gland was not palpable. The breasts were tender, but no masses were felt and the nipples were erect. The heart was normal in size, with no abnormal auscultatory findings. The lungs were clear. Abdominal examination revealed a lower right rectus sear, well healed, with no fascial defects. The liver, spleen, and kidneys were not palpable. There was moderate tenderness in the right lower quadrant, but no mass was detected.

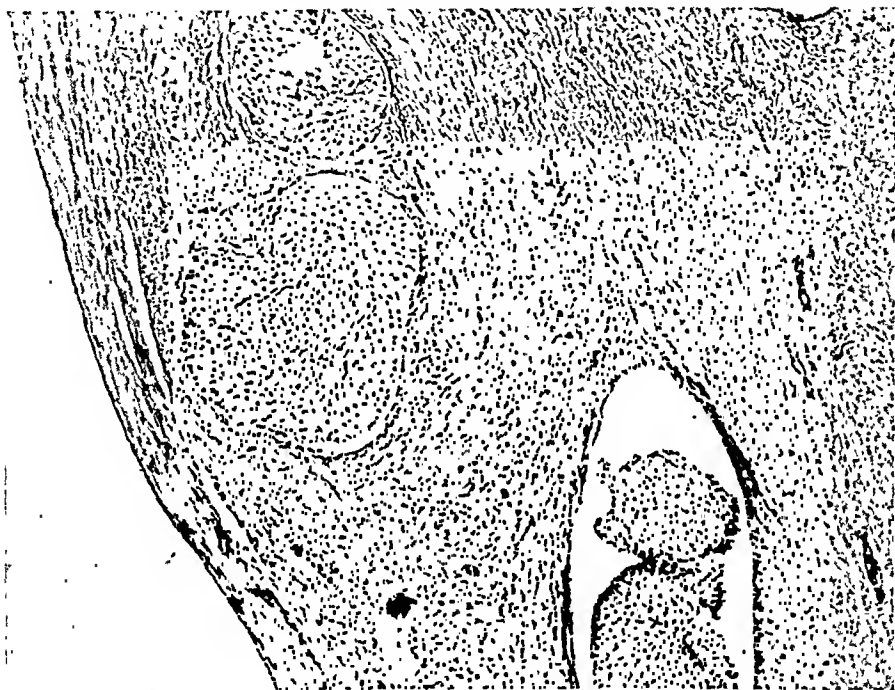


Fig. 1.—Photomicrograph of Brenner tumor wall showing cell rests of Walthard.

Pelvic examination showed a normal distribution of puboperineal hair and the external genitals were normal in configuration. Bartholin's glands and Skene's glands were not palpable. The introitus was parous, with no relaxation of the perineum. The vaginal mucosa was normal. The cervix uteri was firm, movable without pain, and pointed anteriorly. Hegar's sign was positive. Inspection of the cervix revealed no abnormalities. The corpus uteri was retroverted and freely movable, soft, and symmetrically enlarged corresponding to the period of amenorrhea. Anterior and to the right of the uterus was a cystic, nontender, movable mass, approximately 10 cm. in diameter. The left adnexa was not palpable. There was no rectal pathology, and rectovaginal examination confirmed the previous findings. The results of laboratory examinations were as follows: urinalysis, normal; Wassermann reaction, negative; hemoglobin (Sahli), 66 per cent; red blood cells, 3,300,000; and basal metabolic rate, -10.

The patient was admitted to the Emergency Hospital on Aug. 21, 1942, and a laparotomy was performed under avertin-ethylene anes-

By means of the cautery, a dorsal slit is made from the opening of the glans, back for a distance of one-half to one centimeter (Fig. 1), sufficient to permit the foreskin to be pushed back over the corona of the glans, breaking up all adhesions. By cauterizing along the beveled groove of the forceps, the dorsal slit can be made without bleeding or injury to the glans.

The foreskin is then grasped with an Allis forceps at the point where the dorsal slit was begun, approximating the two cauterized surfaces and the foreskin drawn downward. The required length of redundant foreskin is then clamped diagonally from below upward, the beveled surface of the jaws facing the glans. The median ventral raphe serves as a guide in placing the clamp symmetrically on the foreskin. The forceps should grasp more of the foreskin on the dorsal than on the ventral surface.

Since the beveled jaws of this forceps meet along a very narrow line of approximation, there is practically no recognizable line of crushed tissue to be seen after removing the forceps.

The distal redundant foreskin is then removed by cauterizing close to the upper unbeveled side of the forceps (Fig. 2). The crushed cauterized mucocutaneous border is then pushed back over the glans and the mucous membrane and skin are united at 12-3-6 and 9 by fine catgut, or suturing may be omitted if the skin and mucous membrane adhere. The wound may be protected for twenty-four to forty-eight hours by borated vaseline on flat gauze. Healing is very rapid and the ultimate result excellent.

1259 CLIFTON ROAD, N. E.

Boys, Floyd: The Prophylaxis of Peritoneal Adhesions, Surgery 11: 118, 1942.

Based on a careful study and analysis of 188 contributions selected from the world's literature, Boys presents a most exhaustive survey of available information on all the various aspects of peritoneal adhesions. Systematic arrangement of recorded findings in clinical observations and of results reported from experimental work readily convey to the reader a clear picture of the present status of this complex and important surgical problem.

The writer's final summary includes the following statements of facts and suggestions for further study: Up to the present only one prophylaxis has been established against peritoneal adhesions, namely, minimization during operation of all forms of peritoneal damage and avoidance of intraperitoneal infection. The evidence presented from the literature suggests that the use of heparin at present is the most promising supplementary prophylactic measure. It is the only substance proposed which is native to the body, but it does carry the definite risk of hemorrhage. Failure to prove the effectiveness of any measure probably often is due to insufficient laboratory study, which should be continued not for a few months but for years. It will be necessary to investigate other anticoagulants, the absorbable membranes, the sulfonamides and so forth. As preliminary to such studies, acceptable techniques must be developed for standard adhesion production. Clinical evaluation of any measure depends on wider experience and careful examination of findings during a relaparotomy or at post mortem. Reports must be based on large numbers of cases and obviously will require years to accumulate.

HUGO EHRENFEST

CIRCUMCISION OF THE NEWBORN INFANT BY CAUTERIZATION

E. D. COLVIN, M.D., AND R. A. BARTHOLOMEW, M.D., ATLANTA, GA.

CIRCUMCISION of the newborn infant by the cauterization method, described below, has proved to be an ideal procedure, inasmuch as it eliminates loss of blood, prevents infection, minimizes trauma, and secures an excellent cosmetic result, by a technique which is both time-saving and simple.

In addition to mosquito forceps, scissors, an Allis forceps, a small needle and 000 plain catgut, the essential instruments are an electric cautery and a special hemostat for clamping the foreskin. This hemostat can be made by beveling the jaws of an ordinary medium size straight hemostatic forceps at about forty-five degree angles, with an emery wheel, until the jaws meet along a very narrow line when clamped. This insures a minimum of crushed tissue when the clamp is applied and prevents injury to the glans.

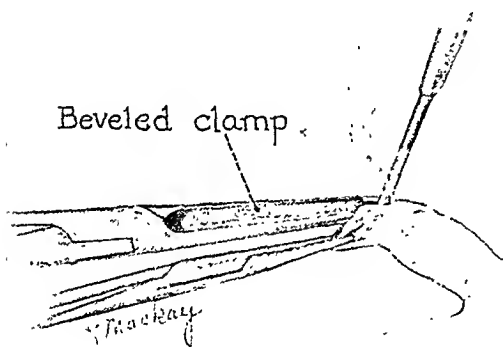


Fig. 1.

Fig. 1.—Dorsal slit by cauterization along groove of beveled clamp to permit retraction of foreskin and freeing of adhesions.

Fig. 2.—Removal of redundant foreskin by cauterization along smooth side of beveled clamp. Operation rendered bloodless by cautery and clamp.

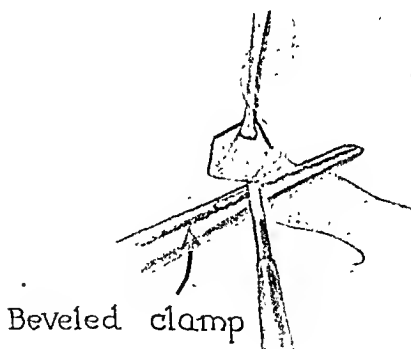


Fig. 2.

After cleansing the genitals with soap and water and draping the field of operation, a curved lubricated mosquito forceps is passed into the opening of the foreskin between the glans and prepuce and repeatedly spread until the glans is freed from the foreskin on its upper surface.

The special forceps is then passed, beveled side up, between the foreskin and upper side of the glans, the foreskin being steadied by traction with a small straight mosquito forceps which grasps it at the tip of the ventral median raphe.

by a short, lucid, and very original text. The macroscopic appearance of tumors are not illustrated but the entire clinical aspects, such as frequency, age incidence, gross pathology, clinical signs and symptoms, malignancy, and benignancy, and proper method of treatment are contained in the text, which, to some degree, is based on lectures given by the author to her students at the University of Padua and considerably influenced by the Vienna school of pathology, particularly that of Schiller.

The classification of ovarian tumors is based on developmental origins as far as is possible. It is in the main original and yet neither bizarre nor too heterodox. In brief, it includes neoplasms developed from the follicle, the mesenchymal core of the ovary, those from totipotent cells, then from structures of extrafollicular portions of the ovary. Other tumors are derived from structures adjacent to the ovary in the adult stage but in close connection with the embryonal ovary (Müllerian, Wolffian and enteric tissues); finally, secondary ovarian growths. On the whole, the classification is clear and can actually be followed out in the pathology. Of special interest is the "endosalpingioma" which the author ascribes to Müllerian derivatives of tubal origin. Such tumors have previously been classed under many different names, perhaps the most striking of which is the papillary cystadenoma. Twenty per cent of ovarian neoplasms, according to Barzilai, fall into this group. They are the tumors which defy cytologic classification of malignant or benign, and have proved a puzzle to the gynecologic pathologist. Another group is the mesenchymoma which contains specific structural units of embryonal glomerulus, the tumor cells being of endothelial type.

The fifty-eight plates, many in colors, are of exceptional excellency. The majority of the black and white microphotographs, well chosen, striking specimens, magnificently reproduced.

The Atlas should prove of great value to gynecologic pathologists as well as to pathologists whose material is scantier and who will find a means of ready reference which can only be replaced by a large slide collection acquired over many years. The marginal headings add greatly to the facility of reference. Although the literature is frequently alluded to throughout, there is no bibliography. It is rare today to see a book so well illustrated as this Atlas.

R. T. FRANK.

The last ten or twenty years have brought a surprising number of discoveries in what appeared to have been the thoroughly studied field of the morphology of ovarian tumors. This has stimulated a general review of the pathologic material in the ovarian tumor collections of many institutions and a reappraisal of related clinical problems. The studies of these years are now culminating in more definitive works on the subject of ovarian neoplasms.

Ovarian Tumors⁴ by Samuel H. Geist, Attending Gynecologist at the Mt. Sinai Hospital is such a work. It is based on the study of over 1,100 cases of benign and malignant ovarian tumors and a thorough review of the recent and much of the early literature. With this material the author presents a comprehensive picture of the subject as a whole with detailed consideration of the clinical and pathologic characteristics of each of the many special types of ovarian tumors.

The practical aspects of the subject have been stressed. Each variety of ovarian tumor is presented with excellent illustrations of gross and microscopic preparations. The latter will be of special service to the pathologist in aiding him to classify his own material. Correlated description of the clinical aspects of each tumor has resulted in this being much more than a mere pathologic treatise. The bibliography is sufficiently ample to make this book a valuable work of reference for the preparation of manuscripts for publication.

⁴**Ovarian Tumors.** By Samuel H. Geist, M.D., Attending Gynecologist, Mount Sinai Hospital; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University. With 312 illustrations. 527 pages. Paul B. Hoeber, Inc., New York, 1942.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

The Hormones in Human Reproduction¹ by George W. Corner is based on the Vanuxem Lectures delivered at Princeton in 1942. These lectures are designed for the laity. Corner has fulfilled the task of making the well-educated lay person understand the very complicated phenomena of reproduction. In doing so he has gone into great detail and built up a foundation based on the lower forms, with gradual transition to human reproduction. In fact the presentation is so thorough that the medical student and the physician will find the lectures valuable and informative, particularly as they are well illustrated by numerous plates and figures, many of which are not readily accessible without minute search of the literature. The author has given a very human touch to his presentation by introducing the history of the various researches; his contacts with the investigators, and his own difficulties, troubles and joys which are so frequent in borderline research. This book is a valuable contribution to this large and interesting field.

R. T. FRANK.

Zondek and Sulman, in the monograph **The Antigonadotropic Factor²** have discussed the entire subject of acquired resistance to hormones. This discussion was initiated by Collip's observation that response to the prepituitary factors diminish progressively with continued injections. His interpretation that this was due to "antihormones" has encountered considerable opposition. The authors give an historical review as well as a discussion of previous work by others. The main portion of the monograph deals with the large amount of experimental work which they have performed, some published, some previously unpublished, to clarify the subject. Like many others, they are unable to accept Collip's interpretation. In their work they have tried to obtain similar types of reactions with other hormones. It is evident that the prepituitary secretions elicit this phenomenon more clearly than any of the other hormones, and that it is strictly limited to those hormones which appear to be combined basically with protein. They conclude that the reaction is an immune one, but that it is not demonstrable by any of the usual serologic methods. They sum up the subject in saying that "the gonadotropic factor represents a new type of blood substance which, though closely related to the immune bodies, does not give the in vitro reactions which generally characterize an antibody." While this work is extremely valuable, careful, and reliable, I am unwilling as yet to accept it as final or conclusive.

R. T. FRANK.

The Atlas of Ovarian Tumors³ by Gemma Barzilai gives a systematic and complete survey of ovarian tumors. It forms a diagnostic atlas complemented

¹**The Hormones in Human Reproduction.** By George W. Corner. 265 pages. Princeton University Press, Princeton, 1942. (London: Humphrey Milford, Oxford University Press.)

²**The Antigonadotropic Factor.** With Consideration of the Antihormone Problem. By Bernhard Zondek and Felix Sulman, Hebrew University, Jerusalem. 185 Pages. The Williams & Wilkins Company, Baltimore, 1942.

³**Atlas of Ovarian Tumors.** By Gemma Barzilai, M.D. Prefaced by Fred W. Stewart, M.D., Pathologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City. 261, pages. Grune and Stratton, New York, 1943.

covers the entire subject of gynecologic as well as obstetric conditions frequently encountered by the gynecologist. He is evidently an experienced teacher and therefore knows how to present the facts simply. The concluding chapter on the more commonly used operations for gynecology is an epitome of the various steps useful for student review. The illustrations are excellent, particularly the careful line drawings.

There are numerous statements which will not be agreed to generally. For example: The exaggerated importance ascribed to dysmenorrhea due to retroflexion as well as the treatment of this syndrome by viburnum prunifolium or by thyroid extract. That the removal of a hypertrophied cervix in prolapse plays a role by lessening the weight of the uterus, is far from convincing. In dealing with gonorrhea, the subject is somewhat beclouded by taking up the various localization points separately in detail.

R. T. FRANK.

The eleventh volume of the *Transactions of the Pacific Coast Society of Obstetrics and Gynecology*⁷ reflects the splendid use of clinical material and the fine scientific work being done on the west coast. The volume opens with a discussion on the "Specific Interacting Substances of Eggs and Sperm" by the guest speaker, Dr. Albert Tyler at the annual meeting in 1941. Dr. Tyler concludes this very interesting paper by stating that certain specific substances, extractable from eggs and sperms from various animals, are complementary proteins and interact as in serologic reactions between antigens and antibodies. Concerned with the initial stages of fertilization process, their specificity of action can count in part, at least, for the degree of species and tissue specificity exhibited in fertilization.

The subject matter of a Symposium on Cancer and one on Infertility covers both the research and practical aspects of these two topics. There are several other excellent presentations. The address of the President, which closes the transactions, is an historical sketch on the Development of the Various Oxytocic Drugs.

This volume marks the end of the first ten years of this organization and from a perusal of the transactions it would seem that such a regional organization must have played a great part in the development of ideals of this speciality in the western part of the United States.

PHILIP F. WILLIAMS.

De Souza Rudge, in a bulky monograph, describes the *Treatment of Urogenital Fistulae by the Flap-Splitting Method*. The preface is written by De Moraes Barros, the chief of the service, which is the Gynecological Clinic of the Medical Faculty of the University of San Paulo, Brazil.⁸ In the course of twenty years, 122 patients with fistulas have been operated upon. One hundred and three of the fistulas were due to obstetric causes (fifty ascribable to necrosis) and only eleven were of gynecologic origin (postoperative). A short, detailed description of each of the cases is appended.

Spinal anesthesia was used throughout. Stress is laid on full exposure of the fistula, if necessary by liberal Schuchardt incisions. The vaginal flaps are mobilized by a T-shaped incision and the fistulous edges approximated by two layers of double zero catgut, followed by closure of the vaginal defect. Of the 104 cases described, 75 per cent were cured. The casuistic includes every conceivable type of fistula. Colored plates illustrate the operative procedure.

R. T. FRANK.

⁷*Transactions of the Pacific Coast Society of Obstetrics and Gynecology 1941. Volume XI. 177 pages. Western Journal of Surgery Publishing Co., Portland, Oregon, 1942.*

⁸*Tratamento Das Fistulas Uro-Genitais pela plástica Do Desdobramento. By W. De Souza Rudge, Livre-Docente de Clínica Ginecológica da Faculdade de Medicina da Universidade de S. Paulo. Prefácio do Prof. N. De Moraes Barros, Catedrático de Clínica Ginecológica da Faculdade de Medicina da Universidade de S. Paulo. 225 Pages. Livraria Ateneu, José Bernardes, Rio de Janeiro, 1942.*

No present classification of ovarian tumors can be universally satisfactory and Geist has accepted in advance the probability of criticism by offering a classification of his own. The classification, to this reviewer, seems so expanded as to present an unusually formidable appearance. In addition, the Geist plan of subdivision continues to utilize some unproved hypotheses of histogenesis to form the basis of major subdivisions. The distinction between "surface" and "subsurface" origin is an example in point, since the origin of pseudomucinous tumors, at least, from the surface endothelium is not finally accepted. The classification also seems unduly encumbered with varieties of sarcomas, peritheliomas and other tumors whose very existence is now in considerable doubt. These are, however, objections based on viewpoint and are not errors in fact. The book remains one of the best available sources of information on ovarian tumors and one which is certain to be of value both to the gynecologic surgeon and pathologist.

HOWARD C. TAYLOR, JR.

The fourth edition of Curtis' *Textbook of Gynecology*⁵ has appeared within four years, bespeaking the popular approval of this work. The new edition shows extreme care in revision, with incorporation of all the newer discoveries which have occurred during this period.

The already excellent chapter on anatomy has been enlarged by the addition of a number of beautiful dissections, including those of the pelvic autonomic nervous system. The entire volume has almost one hundred additional illustrations. All of the gross illustrations are from the artistic pen of Tom Jones. Every chapter has been carefully gone over and revised. The one dealing with the present status of endocrine therapy is short, conservative, sane, and to the point. Although the American trend for treatment of carcinoma of the cervix by means of radium is approved and accentuated; an excellently illustrated description of a modified radical operation for abdominal removal of carcinoma of the uterus is pictured. The treatment of gonorrhea has been entirely revised in accordance with the discovery that the sulfa drugs have proved so sovereign in the cure of this disease in the female. I am in full accord with the advice to discard or limit the local treatment of gonorrhea to the minimum. I likewise agree with Curtis' opinion which "indicates that operation for eradication of infection is rarely necessary . . ." but disagree heartily with the opinion that "surgery, when resorted to, should be directed to reconstruction of tissues laid waste by disease rather than to removal of organs for the purpose of stamping out infection." In my experience, if operation is indicated, except when it involves the mere drainage of purulent accumulations, a very radical removal cures the patient, while less radical measures rarely improve the symptoms.

I would suggest that in mentioning the value of the sedimentation test for the diagnosis of ectopic pregnancy, some indication of what changes occur in that disease should be added, and that a reference to it should also be put in the index. On the whole, I know of no book in the English language which covers the subject of gynecology more completely and satisfactorily within short compass than that of Curtis.

R. T. FRANK.

Essentials of Gynecology by Cooke⁶ is a students' textbook covering the entire subject. The anatomy is well dealt with, chiefly because excellent reproductions of Peham and Amreich's colored plates have been used as illustrations. These illustrations are at present difficult to obtain and therefore have a great value. The author

⁵A *Textbook of Gynecology*. By Arthur Hale Curtis, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School; Chief of the Gynecological Service, Passavant Memorial Hospital, Chicago. Fourth Edition, Reset, with 401 illustrations chiefly by Tom Jones. 723 pages. W. B. Saunders Company, Philadelphia, 1943.

⁶*Essentials of Gynecology*. By Willard R. Cooke, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Texas. 474 pages, 197 illustrations, including 10 in color. J. B. Lippincott Company, Philadelphia, 1943.

resemble a cumulative year book. The present edition includes a new chapter on postnatal care as well as some revision of chapters dealing with the sex hormones. It likewise includes our knowledge of the sulfa drugs and their use in therapy.

Judging by the bibliography, many important new articles have not been included. The authors are somewhat overoptimistic about the effect of estrogens followed by progesterone in the cure of secondary amenorrhea. That the book fills a definite want is apparent from the fact that it has gone through five editions since 1926.

R. T. FRANK.

Miscellaneous

The bound brochure entitled *The Author, Publisher, Printer Complex*¹³ by Robert S. Gill was evidently written by a veteran in the publishing business. It should prove of utmost interest, particularly to budding authors, but can be read with pleasure and profit by the most experienced and blasé writer. It is written in a pleasant though not flippant vein by someone who is evidently disabused by his numerous contacts with authors some of whom must have shown the prima donna complex.

The relation of author, publisher, and printer is defined and this covers much of the business of bookmaking. The author is the supplier; the printer is the manufacturer; the publisher is the merchandizer. Each has his rights and duties. The cost of printing includes only about one-fourth to one-fifth of the price. Binding plays but a small role in the entire expense, and therefore in this country books are solidly bound rather than in paper covers. The publisher in dealing with authors, knows that "The well-known name is in itself an advertisement" but that does not mean that an unknown cannot make himself heard if he has something worth while to say. Sometimes, to bridge the gap, a well-known figure is selected to write a foreword, but it should be remembered that "There are those so much sought after as introducers, and so amiable, that their forewords are worth precisely nothing at all."

The subject of royalty can prove a stumbling block between an unreasonable author or a grasping publisher. It should be remembered that "a fair royalty is not one that emerges from a compromise between the publisher's cupidity and the author's insistence on his rights, but one that it is reasonable to suppose the customer is willing to pay." The author may prefer to be a co-publisher by making contribution to the cost of publishing. If so, his royalty naturally is increased because he is taking a share of the expense and of the risk.

In the concluding chapter, Gill speaks of incomplete manuscripts which add greatly to the tribulations of the publisher and printer as well as adding to the costs. He shows what "bad" copy consists of and what "fair" copy is. He details the various methods of improving copy, making corrections, printer's changes, etc. Then he deals with the ends and oddments such as the preliminary pages and the index, and concludes this very informative pamphlet with guidance about illustrations.

R. T. FRANK.

The increasing longevity of our population emphasizes the medical care of old people. Since the number in the higher age brackets has become constantly greater in recent years, and doubtless will continue to do so in the future, such a book as *Internal Medicine in Old Age*¹⁴ by Dr. Mueller-Deham and Dr. Rabson should be

¹³*The Author, Publisher, Printer Complex.* By Robert S. Gill. 76 pages. The Williams & Wilkins Company, Baltimore, 1940. Reprinted in 1941.

¹⁴*Internal Medicine in Old Age.* By Albert Mueller-Deham, M.D., Associate Visiting Physician, Welfare Hospital for Chronic Disease, etc., and S. Milton Rabson, M.D., Assistant Professor of Pathology, New York Post-Graduate Medical School, Columbia University, etc. 396 pages. The Williams & Wilkins Company, Baltimore, 1942.

Salerno's short monograph submitted as a doctorate thesis, at the University of Buenos Aires, deals with **Hematosalpinx of Non-pregnancy Origin**.⁹ Bazy, in 1910, gave the syndrome the name of "Paquisalpingitis Hemorrhagica." According to Salerno, Bazy described three cases, and Paucot and Bédérine another case. He has found no other references to this syndrome in the world literature. He personally observed four cases. According to the author, the pathology is based on chronic, inflammatory lesions of the genitals, affecting particularly the local vascular system.

R. T. FRANK.

The Lying-in Hospital of New York was founded in 1799. It has been in continuous existence but at intervals has seen radical reorganization. The second edition of a **Handbook of the Lying-in Hospital**¹⁰ which is now the Woman's Clinic of the New York Hospital, should prove of interest to many, in addition to obstetricians and gynecologists, as it contains in brief outline the organization, practice, therapy, and general diagnostic methods in use at this hospital, including the duties of the resident staff, the students, and the nurses. It covers the routine and the techniques. It was primarily designed to help complete co-ordination between doctors and nursing staff, applying both to obstetric and gynecologic patients. It covers such subjects as the entire survey of a normal woman in labor, from her entrance into the hospital until the completion of her stay, and similarly treats the gynecologic patient. In its pages will be found such diverse subjects as the blood bank, the routine for scrubbing up, the method of collecting various bloods and urines for special tests, sample menus, the management of special cases, and the details of every procedure that is used, for example, details of postoperative catheterization. While no attempt at dogmatism is made, the methods that are at present in use in the Lying-in Hospital are given. The booklet is short, concise, and contains a huge amount of information, readily accessible and clearly stated.

R. T. FRANK.

In this study, **Group Differences in Urban Fertility**¹¹ which has been derived from a national health survey, certain conclusions are drawn regarding the subject of population increase in various areas. One notes that the fertility rates of white, foreign married women are now a little higher than those of native, white, married women of urban areas, and that urban Negro marriages are more and more characterized by low fertility levels. The class differences are shown to have marked effect on both the fertility and reproduction rates. A high pregnancy wastage is noted among urban, white women of all classes. There is a thorough consideration of the problems relating to fertility and population policies but no formula for encouraging more babies is brought out. It would seem from the philosophic discussion presented that a social program in its broadest sense would be necessary to increase reproduction on a voluntary basis. This book should be of interest to those who are concerned with the various problems of population and reproduction.

PHILIP F. WILLIAMS.

The **Recent Advances in Obstetrics and Gynaecology**¹² by Bourne and Williams has appeared after an interval of three years. As the authors suggest in their preface, it does not exactly include only "recent advances" but appears to

⁹*La Paquisalpingitis Hemorrhagica. Tesis de Doctorado. By Enrique V. Salerno. 73 pages. Cayetano Vergara, Buenos Aires, 1942.*

¹⁰*Handbook of the Lying-in Hospital. 158 Pages. Woman's Clinic of the New York Hospital, New York, 1942.*

¹¹*Group Differences in Urban Fertility. A Study Derived from the National Health Survey. By Clyde V. Kiser, Member Technical Staff, Milbank Memorial Fund. 284 Pages. The Williams & Wilkins Company, Baltimore, 1942.*

¹²*Recent Advances in Obstetrics and Gynaecology. By Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to St. Mary's Hospital, etc., and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc. Fifth Edition, with 72 illustrations. 363 pages. The Blakiston Company, Philadelphia, 1942.*

last 20 pages are devoted to physical charts and methods which were made by Paterson and Parker in Manchester, England, and by Edith Quimby and her co-workers in New York. These tables and charts are invaluable to the radiotherapist who outlines treatment for each individual case in contradistinction to those who treat by rule of thumb or on empirical basis.

The basic techniques described agree in the main with those conventionally used in modern radiotherapy clinics. They establish a ready reference for the sound treatment of any benign or neoplastic lesion. Naturally variations in equipment and individual needs will require adjustments. For instance the radium therapy is done with element needles and tubes. Many clinics would use radon implants where the element is not available or for greater flexibility, as the case may be in bladder cancers. Exception is taken to the statement on page 45, where the author says "Diagnostic curettage is desirable when radium treatment is planned but is not essential in x-ray therapy." It is a universal teaching that diagnostic curettage should precede all forms of radiotherapy in uterine bleeding. Arrangement of the table of contents alphabetically would facilitate the use of this manual.

WILLIAM HARRIS.

Society Transaction

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 24, 1942

The following papers were reported:

Case Report: Multiple Pregnancy, Pyelonephritis, and Septicemia. Joseph Harris, M.D.

Cerebral Complications Occurring in the Toxemias of Pregnancy. John Parks, M.D., and Jed W. Pearson, Jr., M.D. (For original article, see page 774.)

Psychiatric Observations on Forty Cases of Induced Abortion. Beatrice B. Berle, M.D. (by invitation).

welcome not only to specialists in internal medicine but to all those whose practice will bring them in contact with the older or senile patient. The discussion in the text is limited to internal medicine in old age and embraces the status, problems, difficulties, and other broad components of geriatric medicine. Of particular value to the gynecologist is the section dealing with the urogenital system in the aged female.

PHILIP F. WILLIAMS

The Connecticut Medical Society has performed a useful task in compiling the series of articles, *The Essentials of Emergency Treatment*,¹⁵ dealing with the problems of emergency practice which may arise during a period of war. The subject matter describes the types of injuries which may follow the effects, directly or indirectly, of any type of bombardment or destruction. After such general topics as "Organization of Emergency Medical Associations in the Community," there are articles on shock, chemotherapy, blood transfusions, and emergency field treatment. Regional injuries are then taken up seriatim. These are well worked up and concisely presented, and a reading of this book should prepare the civilian professional services very well for the part they might be called upon to play at any time. It is of some interest that no mention has been made of emergency obstetric complications.

PHILIP F. WILLIAMS.

The fourteenth semicentennial edition of Osler's *Principles and Practice of Medicine*,¹⁶ originally written by Dr. Osler, is presented by Dr. Henry A. Christian, the present editor. This classic text has guided many generations of medical students. The influence of the fine men who have previously edited the book have mellowed its teachings.

In the present edition, in which much new material has been added, the text shows a considerable re-arrangement. Osler's *Practice in Medicine* belongs on the handy book shelf of every obstetrician, since constantly through the pages reference is made to the influence of pregnancy on one disease or another, or the complicating effect of various medical conditions on the reproductive functions.

PHILIP F. WILLIAMS.

This *Manual of Radiotherapy* is an outline of the basic x-ray and radium techniques employed in the radiotherapy department of the Presbyterian Hospital in New York.¹⁷ Its purpose, as stated both in the foreword and in the introduction, is for guidance of the departmental residents and for students at the beginning of their work in this specialty. The author stresses quite correctly in the introduction that no hard and fast rules can be made for any individual situation, that variations in lesions and in the general condition of the patient will often call for modification of basic technique.

Practically all pathologic conditions both benign and malignant that are amenable to radiotherapy are discussed. There is a brief description of the signs, symptoms, histopathology and in some instances of the differential diagnosis of the various topics; this is followed by an outline of the basic radiotherapeutic technique. The

¹⁵*The Essentials of Emergency Treatment*. Edited by Herbert Thoms. 144 pages. Published by The Connecticut State Medical Journal, New Haven. Printed by The Whaples-Bullis Co., Inc., New Haven, 1942.

¹⁶*The Principles and Practice of Medicine*. Originally written by Sir William Osler, Bart, M.D., F.R.C.P., F.R.S. Designed for the Use of Practitioners and Students of Medicine. By Henry A. Christian, A.M., M.D., LL.D., Hon. Sc.D., Hon. F.R.C.P. (Can.), F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Fourteenth, Semicentennial (1892-1942) Edition. 1,475 pages. D. Appleton-Century Company, New York, 1942.

¹⁷*A Manual of Radiotherapy*. By Murray M. Friedman, M.D., Assistant Professor of Radiology, College of Physicians and Surgeons, Columbia University; Assistant Radiologist, Presbyterian Hospital, New York, N. Y. With a foreword by Maurice Lenz, M.D. 86 pages. Edwards Bros., Ann Arbor, Mich.

series) and seven (29 per cent) were alive five years. Twenty received "inadequate" radiation dosage and two (10 per cent) survived five years.

The major factor in prognosis and determination of type of therapy to be employed is the clinical stage of progression of disease. Morphologic classification and histologic grading appear to be of minor importance. Maximal dosage of radiation therapy should be employed whenever possible.

J. P. GREENHILL.

Cosbie, W. G.: Carcinoma of the Vulva, *Canad. M. A. J.* 43: 439, 1940.

Carcinoma of the vulva is a disease of later life. Neglect of symptoms results in an unnecessarily high percentage of advanced cases. In the author's opinion radical vulvectomy offers a hopeful prognosis. Simple vulvectomy and indifferent gland excision have no place in the cure of carcinoma of the vulva. Radiotherapy is of value in the treatment of elderly patients.

J. P. GREENHILL.

Berven, Elis G. E.: 177 Cases of Primary Vulva Carcinoma, *Acta Radiol.* 22: 99, 1941.

Berven reviews the treatment of carcinoma of the vulva and reports the results of operation. (According to comprehensive collective statistics the percentages of five-year cures are 4 to 10 per cent, some hospitals report five-year cures in 17 per cent or 35 per cent of the cases studied, and Taussig reports a five-year cure of 65 per cent.) The percentage of five-year cures attained with radiologic treatment is 11.9 per cent. At the Radiumhemmet a five-year cure of 13 per cent was attained.

Since 1922 carcinomas of the vulva are treated at the Radiumhemmet by electrocoagulation of the tumor of the vulva combined with telerradium treatment of the glandular regions and eventual dissection en bloc of the glands in cases amenable to surgical intervention. Among 177 cases of primary carcinoma of the vulva 65 cases, or 36.7 per cent, were alive five years or more free of symptoms. If there is no clinical evidence of metastases (Stage I), it is advisable to treat the glandular regions by telerradium and to perform dissection not before clinical evidence of metastases has been noted. In this stage, 59.3 per cent of the cases were free of symptoms for a period covering five years. Cases presenting clinical metastases (Stage II) should be treated by telerradium combined with subsequent dissection, if the metastases do not disappear. In this stage freedom of symptoms was attained in 22.9 per cent of the cases for a period covering five years. Cases presenting inoperable metastases (Stage III), should only be treated by telerradium. In such advanced stages dissection does not seem to be appropriate. In this stage freedom of symptoms was attained in 3.8 per cent of the cases for a period covering five years. The percentage of postoperative mortality with electrocoagulation and surgical removal of the glands is only 8.5 per cent.

J. P. GREENHILL.

Newcomer, Elizabeth: Comments on Treatment and Sequelae of Carcinoma of Uterus, *Am. J. Roentgenol.* 45: 651, 1941.

According to Newcomer, fistulas are seldom due to faulty methods of irradiation but to the extension of the disease. Constriction of the ureters, ureteral dilatation and hydronephrosis are also generally due to extension. A dull, nagging pain in the hips, groin or radiating down to the thigh or leg may be caused by ureteral obstruction. Cystoscopy and visualization of the ureters are indicated in such cases. Similar symptoms are caused by extension of the disease to the lumbar and sacral nerves and to the uterosacral ligaments. Masses may form on the side walls

Department of Reviews and Abstracts

Selected Abstracts

Cancer

Morton, Daniel G.: Early Diagnosis and Proper Treatment of Cervical Cancer, J. A. M. A. 118: 271, 1942.

The figures from the University of California Hospital show that two-thirds of the women seeking treatment for cervical cancer had advanced growths. Late diagnosis, then, is the chief limiting factor in achieving significant improvement in results.

The average duration of symptoms in this group of cases was 8.7 months. The earlier the symptoms were recognized the higher was the percentage of cures. Periodic examination is also a possible factor in early diagnosis. The ability to recognize cancer in its early stages is not always an easy one. Schiller's test and the colposcope are aids in the early diagnosis of early carcinoma. The most important procedure is in obtaining a biopsy.

High voltage roentgen ray and radium therapy is the treatment in the vast majority of cases.

WILLIAM BERMAN.

Hoffman, Paul E.: Ureteral Obstruction Following Irradiation of Cancer of the Cervix, West. J. Surg. 50: 69, 1942.

Ureteral obstruction with consequent ureteral dilation, hydronephrosis, loss of renal function and a terminal uremia is the most frequent cause of death in patients suffering from Stage III and IV cervical cancer. Intensive ureteral dilatation of the affected ureter as a means of alleviating this condition has proved disappointing, and other methods will have to be devised.

These are the author's conclusions based on a study of 97 patients with cervical cancer.

HUGO EHRENFEST.

Walter, Robert I., Bachman, Arnold L., and Harris, William: The Treatment of Carcinoma of the Ovary. Improvement of Results With Postoperative Radiotherapy, Am. J. Roentgenol. 45: 403, 1941.

A clinical classification of ovarian carcinoma according to stage of progression is presented, and the necessity for its use in evaluating therapeutic results is stressed. This material consists of 124 cases of ovarian carcinoma which are reviewed with particular reference to therapeutic results. The primary operative mortality was 9.8 per cent. Sixty-three patients with ovarian carcinoma were treated by surgery alone. Of these, four, or 6.3 per cent, survived five years. Sixty-one patients were treated by surgery plus postoperative radiotherapy. Thirty-one patients received moderately large amounts of radiation (considered as "adequate" in this

Of those patients showing carcinomatous glands, 43 per cent survived as compared to 80 per cent in which the glands were not involved.

Points in treatment: (1) Patients showing a strong positive Ruge-Phillipp virulence response were not operated upon. (2) All patients since 1936 received prontosil. (3) All young women received endocrine treatment the first few post-operative days. (4) Since 1939 roentgen radiation has been given three weeks post-operatively and at the same time 1,000 mg. hr. radium is applied. The vulval and gluteal fields are not neglected. The tendency appears to be toward higher dosage and application closer to the time of operation.

R. J. WEISSMAN.

Kliiver, R.: Latent Portio Carcinoma in Sisters, *Zentralbl. f. Gynäk.* 64: 1219, 1940.

The author gives added evidence of the life-saving value of routine colposcopy. A 44-year-old woman was operated upon for myomas of the uterus and atypical portio epithelium. Nothing in the symptomatology was indicative of the presence of carcinoma. The menses had recently been somewhat prolonged and the patient complained of monthly backache, a symptom of years' duration. Several colposcopic examinations revealed extension of the leucoplakia deep into the cervical canal. Microscopic sections of the operative specimen revealed carcinoma. At the patient's request her sister, aged 43 years, was then examined. Here the colposcope revealed erosion on the anterior cervical lip and an extensive area of soft whitish leucoplakia extending well into the cervical canal. Portio amputation was done and microscopic examination confirmed the presence of cancer. There was no evidence of extension in either case.

R. J. WEISSMAN.

Winterton, W. R.: A Comparison of Results of Surgery and Radiotherapy in Carcinoma of the Cervix Uteri, *Brit. M. J.* 1: 195, 1941.

A series of 179 cases of carcinoma of the cervix seen in patients from 31 to 80 years of age (average age equaled 53.5 years) is presented. Of these cases 152 were squamous celled carcinoma and 7 were adenocarcinoma. All cases deemed operable, except 2, were given the benefits of surgery; the rest were referred to radiotherapy. Of the 64 patients treated with surgery, 5 also had postoperative x-radiation. Of the 115 referred to radiotherapy, 87 were treated with radium (Paris method) and x-rays; 14 by radium (Stockholm method) alone; and 11 were untreated.

The surgical cases were classified in 2 groups; (1) with gland metastasis (2) without gland metastasis. The radiotherapy cases were grouped according to the League of Nations Classification.

The results, based on a five-year survival criterion, show that of the series, 49 survived, giving an absolute survival rate of 27 per cent or a relative survival rate, deducting cases that refused treatment or died of other causes, of 30 per cent.

The author points out the difficulties of accurately comparing the results obtained with surgery and radiotherapy but concludes that in all technically operable cases a higher percentage of five-year survivals has been obtained by radiotherapy than by surgery. There is also a much lower treatment mortality with the former. With technically inoperable cases, a few five-year survivals have been obtained.

FRED L. ADAIR AND W. H. PHILLIPS.

of the pelvis by extension through the parametrium and broad ligaments, causing excruciating pain. Pressure on the veins of the lower extremities may result in edema of the lower limbs and external genitals. Invasion of the rectum may result in stenosis, ulceration, intestinal obstruction, and fistulas. If lower abdominal pain follows radium application, patency of the cervical canal must be established. Roentgen therapy should precede radium therapy. It reduces infection and the size of the tumor, makes the application of radium safer, renders possible the giving of a heavier dose of radium and distributes it more evenly throughout the tumor. Radium should be given in both the uterine and the cervical canals in doses short of tolerance by the surrounding tissues. As large a dose of radium as can be safely tolerated should be applied to the vault of the vagina by means of the bomb, colpostat or interstitial irradiation in selected cases.

J. P. GREENHILL.

Baatz, H.: Influence of Castration on Growth of Carcinoma, *Zentralbl. f. Gynäk.* 65: 472, 1941.

Investigating the hypothesis that castration has an influence on the growth of carcinoma, Baatz implanted adenocarcinomatous tissue in castrated female mice at operation and at intervals of eight to ninety days. Two other groups were first implanted and castrated seven and sixteen days later. Another group in which spontaneous carcinoma was found was castrated. From his study of the tissues the author concludes that in mice, at least, prejuvenile castration would seem to prevent establishment or inhibit growth of mammary carcinoma. On the contrary prophylactic castration in older animals apparently encouraged more rapid growth of the implanted tumor. Castration during the age of greatest ovarian activity, which Baatz terms late castration, also led to increased tumor growth. The author feels that though castration per se will not solve the problem of mammary carcinoma, the solution lies somewhere in the endocrine milieu.

R. J. WEISSMAN.

Hinselmann, H.: Active Proliferation of Capillaries in Early Portio Carcinoma as a New Means of Differential Diagnosis, *Zentralbl. f. Gynäk.* 64: 1810, 1940.

Hinselmann, in attempting to improve his diagnostic accuracy through colposcopy, now makes a special study of the blood vessels to be seen in suspicious areas by sodium vapor monochromatic illumination. An 18x magnification is used instead of the usual 12x. Normal tissue appears an even gray and the small venules can barely be seen. The areas of early carcinoma are whitish, and the small vessels, arterioles as well as venules, may be seen and studied. They appear black, enlarged and quite erratic in their course and distribution. Hinselmann now feels that he can make a positive diagnosis of carcinoma of areas which he would previously have labeled suspicious of carcinoma.

R. J. WEISSMAN.

Hoppe, W.: The Value of Radical Operation as an Elective Treatment of Carcinoma of the Cervix, *Zentralbl. f. Gynäk.* 64: 1126, 1940.

The author shows a five-year survival of 71 per cent of 62 cases of carcinoma of the cervix operated upon from 1930 to 1933. Primary mortality was 8 per cent. The increase of 15 per cent over previous survival figures is attributed to prophylactic postoperative radiation. In women under 40, the five-year survivals are 28 per cent higher in operated than in radiated cases. The author's figures are broken down as follows:

Grade I	43 cases—survival 77%
Borderline	10 cases—survival 80%
Grade II	9 cases—survival 33%

and Government Experiment Stations have been much less extensive as compared to the Russian statistics. Salisbury³ states that the most recent information available with respect to the total number of cattle artificially inseminated in the United States, is contained in a publication of the U. S. Department of Agriculture. This report lists the artificial breeding associations in the United States which were active as of Jan. 1, 1942. This publication⁴ shows that but 64,335 cows were signed up in organizations in which all of the breeding was done by artificial insemination. Salisbury, in his recent communication,³ states that artificial breeding of cattle in the Agricultural Experiment Stations is limited usually to those cattle owned by the stations. He writes, "actually, there are very few cattle artificially inseminated at the agricultural experiment stations," and that the interest of the teaching institutions is centered now on semen physiology.

The attempt to transfer artificial insemination from the field of animal research and experimental curiosity to a legitimate method of treating human sterility, as a sequel to wise selection and careful study, did not meet with much success save in isolated instances.⁵⁻⁷

Rohleder,⁸ in 1924, was able to collect only 123 human cases, artificially inseminated, from the world literature and among these he could unearth but 47 examples of impregnation. Englemann,⁹ in 1928, brought Rohleder's series up to a total of 185 cases with 65 successes. Selorohowa,¹⁰ in 1927, reported on 88 individuals with 33 fortunate results. Seguy,¹¹ in 1935, reported seven successes among sixteen women treated by artificial insemination; while he had published an earlier series of 24 treatments, in a few women, without a single conception. Beardsley¹² reported two pregnancies after using donor semen, but he does not state the total number of patients treated.

Seashore,¹³ in 1938, reviewed the American literature from 1902 on, and was able to discover only twenty-four articles on the subject. He added a single case report. Donor semen was used in his case. Cohen,^{14, 15} Dickinson,¹⁶ Goldberg and Schatz,¹⁷ Israel,¹⁸ and Stokes¹⁹ each added one to six successful cases to the literature. It remained for Cary²⁰ to add the largest single series to the American writings. In one group of 17 women, inseminated one to six times with donor semen, he obtained nine pregnancies; while in 18 additional cases, inseminated with a total of 37 specimens from husbands, he procured only four successful results. Cary is skillful, meticulous, and has had, without doubt, a longer experience with artificial insemination than any other clinician. It is to be noted that his results were much less favorable than those reported by Seymour.²¹ Cary says of the latter author that she "relates unique experiments in this field and she seems to attain results not equalled by other reporters." The writer concurs heartily with Cary in this last statement for, until June, 1941, the date of Seymour and Koerner's more recent report, the total number of successes revealed results which were anything but striking or encouraging.

In 1941 Seymour and Koerner²² astounded students of these problems by bringing forth a paper purporting to summarize the results of a recent survey of the status of artificial insemination in the United States.

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Original Communications

THE STATUS OF ARTIFICIAL INSEMINATION*

A Critical Review

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THE supporting evidence for the success of artificial insemination has been based to a considerable extent upon veterinary practices among farm animals. In fact the placement of male sex cells by artificial means within the genital organs of the female remained chiefly an experimental curiosity in the animal laboratories until Iwanoff¹ considered its practical veterinary value, in Russia, in 1899. This investigator worked principally with horses, obtaining a percentage of conceptions higher than that of natural matings while the reproductive capacity of the stallion was multiplied ten times. Although World War I forced the suspension of his work until 1923, the economic advantages to animal husbandry were not overlooked.

Brewer² states that the Moscow Experimental Station up to 1932 impregnated successfully, by artificial means, two million cows, three million ewes, six hundred and fifty thousand mares and two hundred thousand sows. In a forty-day breeding season it became possible to fertilize four thousand ewes from one ram, and in a period of sixty days twelve to fifteen hundred calves could be sired by a single bull. The experiences of the Artificial Insemination Stations, in this country, under the various animal husbandry departments in our Agricultural Schools

*Presented, by invitation, at a meeting of the New York Obstetrical Society, December 8, 1942.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

the figures presented. He has kindly forwarded the following comments:

"If '9,489 women had achieved at least one pregnancy by this method' and in '1,357 patients (presumably women) more than one pregnancy was effected by this means,' how did it happen that there were records of 'nearly 9,500' 'children sired by this method,' instead of at least 9,489 plus 1,357 which equals 10,846?

"The remark is made that 'more than 97 per cent of all the pregnancies terminated in living, normal babies,' but 10,846 times 0.97 equals 10,521, not 9,489.

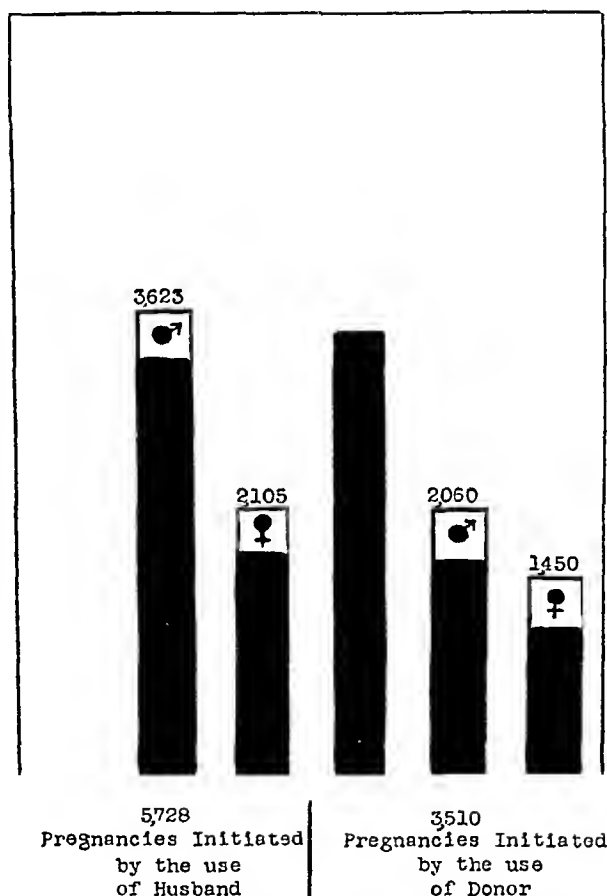


Fig. 1.—(By permission, Journal of the American Medical Association.)

"In Fig. 1 (of the original article) listing 3,623 plus 2,105, plus 2,060, plus 1,450 equals 9,238 'viable pregnancies,' which checked with the '9,238 children conceived,' listed in Fig. 4 (showing geographic distribution in the United States by groups). Now 9,238 divided by 9,489 equals 0.9735 which seemed to correspond to the 'more than 97 per cent' noted above. If we identify 'viable pregnancies' with 'children conceived' this would seem to be a satisfactory check. However, when the distribution of 'viable pregnancies,' listed in Fig. 1 is compared with the distribution of 'pregnancies,' mentioned in the second paragraph,

These authors state that this survey disclosed that "9,489 women had achieved at least one pregnancy by this method." This number is arresting when one considers that it is *approximately twenty-one times greater than that reported in the entire medical literature during the previous four decades!* Perplexity besets the thoughtful readers of that report²² when in the third paragraph they find this astounding statement: "*More than 97 per cent of all the pregnancies resulting from artificial insemination terminated in living, normal babies.*"

Because Seymour and Koerner's experiences and reported findings differ so markedly from the conclusions of other authors, it follows that the contribution of these authors should be subjected to the most critical and impartial analysis. If their report will stand the test of scientific scrutiny it obviously would represent a conspicuous milestone in the management of human sterility. However, because their figures are curiously at odds with the generally accepted conclusions of obstetric statistics, doubt concerning this unconfirmed analysis cannot help arising in many minds. Furthermore, the article²² is undocumented, without a single bibliographic reference, and the findings were such as to be in dramatic contrast to all other reports on this procedure. Competent clinical specialists were forced *ipso facto* to entertain genuine doubt concerning the unique success as disclosed in this report or else question their own professional ability in the treatment of their patients with sterility.

Brewer² states that, "Every year in the United States about 50,000 women leave the marriage altar, later to discover they cannot have children, while about 2,000,000 couples who are of child-bearing age are constantly in that condition." In days of war with its tremendous increase in marriages, an increase in 1941 over 1939 of 304,000 marriages, or 22.1 per cent,²³ the problem of sterility will increase in a proportionate degree to the increase in the actual number of births, an estimated 3.4 per cent increase in June, 1942, over June of 1941.²⁴

In the interest of these many real and potentially sterile couples, in the process of exhausting every possibility of discovering an office method which could be helpful in handling certain carefully selected sterility cases, I have made a critical analysis of Seymour and Koerner's provocative report which appeared in the most widely circulated of medical periodicals, the *Journal of the American Medical Association*.²²

An Analysis of the Seymour and Koerner Mathematics

Dr. L. B. Tuckerman,⁶⁴ a physicist who has merely a layman's interest in biologic problems, noticed this article²² and was interested enough in the unusual ratio of boys to girls therein reported to read it in detail. He was immediately struck by the glaring mathematical discrepancies in

effect conception, are distinctly deleterious as a process involving perpetuity to our race. Perhaps man can populate more efficiently and with greater fetal salvage, quantitatively and biologically, without the distracting pre-occupation of sexual congress!

Mathematical skepticism soars rapidly with the dizzy climb of the ascending limb of the curve seen in Seymour and Koerner's Fig. 3²² (the points in the ascending segment of this curve jump from one locus of intersection, of below 100 cases on the vertical coordinate with ap-

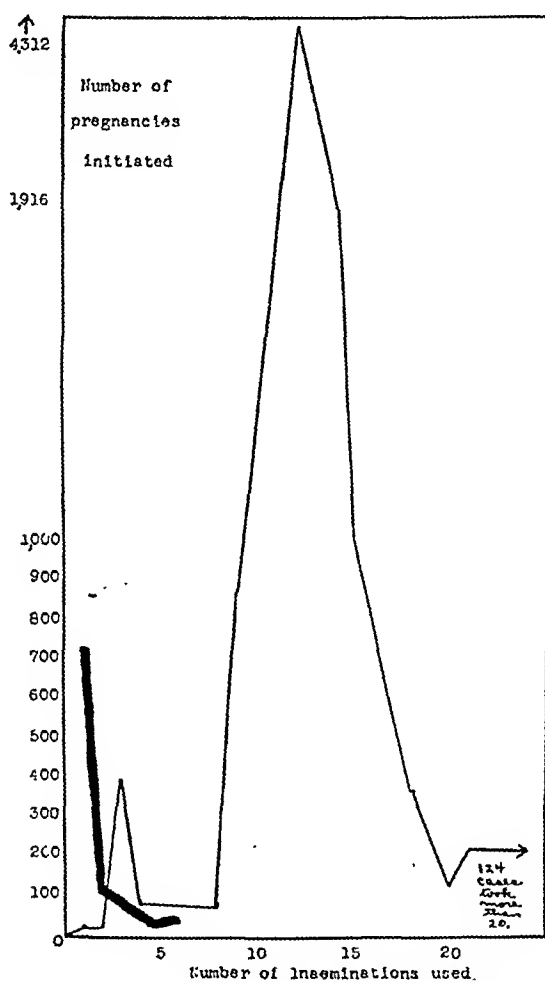


Fig. 2.—(By permission, Journal of the American Medical Association.)

proximately 8 inseminations on the horizontal coordinate, to its succeeding point of 4,312 cases on the vertical axis of the coordinate where it is intersected by the number of 12 inseminations from the horizontal axis). (Fig. 2.) From this curve one would gather that the chance for successful impregnation was approximately 43 times greater upon the occasion of the twelfth artificial insemination than upon the fourth to the eighth insemination. It is impossible to reconstruct a complete curve, using the Seymour and Koerner figures cited in their first table entitled

both amazement and exasperation grow." The comparison is shown in Table I.

"Where did the extra 54 boys come from? Misprint does not explain this inconsistency since the totals noted above are the correct totals of the individual items. Further the first table totals 9,489 while the items listed in Fig. 4 total 9,238.

TABLE I

	HUSBAND SEMEN		DONOR SEMEN		TOTAL
	BOYS	GIRLS	BOYS	GIRLS	
Pregnancies	3,569	2,271	2,107	1,542	9,489
Viable pregnancies	3,623	2,105	2,060	1,450	9,238
Difference	+ 54	- 166	- 47	- 92	- 251

"It may be too much to expect physicians to give a set of figures which will counterbalance, nonetheless it does seem that any comment on the unusual boy-girl ratios noted might better be withheld until the discrepancies in the figures are explained. Incidentally there were no cases of twins reported in this article. It doesn't seem probable that twin births could account for the extra 54 boys for that would assume an even more remarkable distribution of sex ratios. In an ordinary series of 10,000 pregnancies one would expect about 125 pairs of twins. Absence of any comment on this feature makes the reliability of the report seem even more doubtful."

Brunner,²⁵ in a recent survey of 1,556 normal conceptions, reports that but 869 (55.8 per cent) of these fertile matings reached viability. Pregnancy wastage by spontaneous abortion alone, as a single causative factor is high. Malpas²⁶ estimated an 18 per cent loss among his 2,000 fraternities examined; Whitehouse²⁷ found 17.6 per cent; Mall,²⁸ 20 per cent; Brunner and Newton,²⁹ 15.8 per cent; and Stix,³⁰ 6 per cent, terminating in spontaneous or unintentional abortion. Hamilton³¹ states that among 388 women, seen at Bellevue Hospital, there was an aggregate 1,240 pregnancies prior to the current gestation, in this study period, and that 13 per cent of first pregnancies in the previously gravid group ended in spontaneous abortion, while 17 per cent of all pregnancies of a higher order than the first ended in spontaneous abortion. One might compare the above reports with the unusually low total pregnancy wastage, from all causes, which is slightly less than 3 per cent as cited by Seymour and Koerner²² in their article. In Brunner's series²⁵ of 1,556 conceptions achieved by normal coitus, approximately every twenty-third conception resulted in fetal wastage. In Seymour and Koerner's figures, when computed from their own numbers (9,489 - 239 [217 + 22] equals 9,250, divided by 9,489 equals 0.971, minus 1.000 equals 0.029 or 2.9 per cent pregnancy wastage), we find that only the three hundred and forty-fifth conception is claimed to have resulted in fetal loss.

The foregoing discloses a salvage of double the Stix findings, about six or seven times that of Malpas, Whitehouse, Mall, Brunner and Newton, and fourteen times that of Brunner's larger series.

To secure this enormous increase in fetal salvage it would appear, statistically, that the old-fashioned connubial techniques, as practiced to

upon this interesting chart (Fig. 3 of Seymour and Koerner), points out succinctly and with good humor, the obvious inaccuracies leading to the construction of this figure but without going into pedagogical detail. He writes, "One thing that puzzles me is Seymour and Koerner's Fig. 3. Eleven . . . is considered a magic number. Here we have twelve taking its place. Is there any good reason why 12 should be so magically much better than 11 or 13? Maybe 13 is an unlucky number. Looking again at this chart apparently 7 or 11 are the magic numbers, as between them insemination really takes place." . . . "This curve is also a mystery."

It is not unusual to discover that 22,358 doctors (74.5 per cent) failed to reply to the survey letters mailed to 30,000 physicians in this country by Seymour and Koerner. It is, however, most difficult to understand why two of every three of the doctors responding to such a questionnaire, were able to report parallel success with any single medical procedure!

The Medicolegal Aspects of Artificial Insemination

Israel¹⁸ differentiates the techniques using the individual donors furnishing the sperm specimens to the doctor, for artificial insemination, by setting up two descriptive categories, *homologous artificial insemination* using the husband's semen and *heterologous artificial insemination* in which the semen of a nonmember of the family is used. Stepita⁵⁷ had previously (1933) reported a specialized method of heterologous artificial insemination wherein the sperm of the donor was transported to the wife by her azoospermic husband. (The ejaculatory ducts of the husband, possessed of an azoospermic seminal vesicle, are catheterized using a cystourethroscope. Semen from a blood relative of the husband is then injected into the husband's seminal vesicle, under aseptic conditions, and coitus between the married couple is undertaken soon after or within a reasonable time following the implantation of "relative donor semen" within the aspermatic seminal vesicle of the husband. Stepita terms this procedure, "*physiologic artificial insemination*."') For the sake of completeness, the method suggested by Stepita would seem to belong to the heterologous artificial insemination and as a specialized technique under it.

The medicolegal aspects in using the homologous artificial insemination techniques are practically nonexistent. Usually in each case the husband seeks the help of the physician because of his own inability to deliver properly his sperm to the generative tract of his wife or else the latter presents some unusual situation in the vaginal or cervical morphology or physiology. The idea, however, of "boosting the sperm" three inches on their six inch journey, by the homologous artificial insemination method is not recommended.⁵⁸ In such cases the only problem is medical which seldom, if ever, presents medicolegal complications.

Many entangling medicolegal complexities surround the procedure which is less common in general medical experience, heterologous artificial

"Relationship of Pregnancies to Number of Inseminations," because the loci of the coordinates are missing for the ordinates of the fourth, fifth, sixth, seventh, tenth, eleventh, thirteenth, sixteenth, seventeenth, nineteenth order and those beyond the order of the twenty-first insemination.

From Seymour and Koerner's (first) table illustrating the relationship of pregnancies to the number of inseminations, one can calculate the total number of inseminations necessary to secure 9,365 pregnancies (Table II). On the assumption that the "number of pregnancies resulting" from artificial insemination is absolute as related to the "number of artificial inseminations employed," the items in these two columns could logically be multiplied, with the exception of 124 pregnancies resultant from more than 21 inseminations in each case, and the total number of artificial inseminations could be obtained.

TABLE II. RELATIONSHIP OF PREGNANCIES TO NUMBER OF INSEMINATIONS

NO. OF PREGNANCIES RESULTING	NO. OF INSEMINATIONS EMPLOYED	TOTAL NUMBER OF ARTIFICIAL INSEMINATIONS
3	1	3
17	2	34
409	3	1,227
61	8	488
897	9	8,073
4,312	12	51,744
1,916	14	24,908
1,003	15	15,045
367	18	6,606
139	20	2,780
241	21	5,061
124*	21+*	-----
9,365		115,969

*Numbers not included in totals.

This calculable total number of artificial inseminations was 115,969, the number necessary to impregnate successfully 9,365 women. One must also bear in mind that in "1,357 patients more than one pregnancy was effected by this means," hence a reader, who is statistically inclined, would think obviously, was it necessary to employ artificial insemination for the second pregnancy an average of 12 times? One is left with the implication that the No. 12 bore supernatural properties and the preceding 11 artificial inseminations were but part of the ritual to attain eventual ovum penetration by the sperm upon the preternatural "Twelfth Try." It was obvious that such figures based upon such a large series of observations would furnish, to those interested in the problem of artificial insemination, considerable quantities of documentary evidence useful to advance investigation still more in these problems.

The author was not alone in his interest in this unique table and figure³ as portrayed by Seymour and Koerner. Dr. Robert C. Cook, editor of the *Journal of Heredity*, in a letter to Dr. Alan F. Guttmacher (both individuals^{32, 33} giving permission to use excerpts), in commenting

comes a medical curiosity. She is envied by the primitive and wanton-minded, pitied by those gifted with easy fertility, shunned by her relatives and perhaps unfortunately by her own child. The so-called veneer of civilized culture is thin, none the less it is of an oppressive nature to the woman willing to overstep the bounds of her environmental social mores and wedlock in her real desire to have children of her own.

The donor's health, genetic background, fertility history, age, character, physical characteristics, temperament, blood type⁶⁰ in addition to the minor factors of religion, sociologic environment and intelligence quotients must be evaluated with meticulous care if the newborn is to be received in the barren couple's home, and they are all to become sociologically and psychologically adaptable one to another. Let it be reiterated—if we, as physicians, were to spend as much time seeking more causes of relative infertility, as some do in seeking suitable donors, there would be much less necessity to utilize heterologous artificial insemination. As doctors, our function to our sterile patients is more correctly prevention and reparation, not substitution and temporization.

Physiologic Considerations

Recent investigations have advanced considerably the progress in methods to determine disturbances in human fertility.

Rubenstein⁶¹ reported new data upon sperm survival in vivo, in one instance 25.5 hours in utero postcoitus. MacLeod has spent four years³⁷⁻³⁹ studying the metabolism of the male sex cells. He was the first to report that their motility was dependent upon a process of anaerobic glycolysis. With Hotchkiss, he has successfully adapted this laboratory finding to two sterile marriages. In both instances the wives became pregnant following the use of intravaginal isotonic glucose in Ringer's solution taken as a douche prior to coitus. Lamar, Shettles and Delf⁵⁰ established the point that cervical mucus possesses cyclic periods of refractivity and penetrability to spermatozoa. Huggins⁴⁶ reports that the seminal fluid requires certain electrolytes if sperm motility is to be maintained. Shettles⁵⁵ has contributed valuable data relevant to the correlation of dietary deficiencies to male infertility, although no report exists as to its potential possibilities in preventing male infertility. The latest report of MacLeod and Hotchkiss⁶⁷ discloses that it is possible that azoospermatic males (the principal indication for heterologous artificial insemination), especially those whose azoospermia may be due to occlusion of the ductus deferens, can have adequate spermatozoa formation below the point of obstruction. The concentration of glucose in the local tissues and media in such cases may be within the normal range. The last physiologic finding is pertinent in that glucose acts to provide maintenance of motility and survival of sperm, pending the development of technical means to overcome their blocked means of egress. These technical steps are being investigated at this time.

insemination. Regardless of the actual technique employed (simple placement of donor semen against the portio vaginalis and in the posterior fornix; delivering donor semen into the cervical canal or uterine cavity with a large caliber needle or permitting the husband to act as a physiologic "messenger boy," carrying donor semen in his azoospermic seminal vesicle, to his wife), all methods using heterologous donor specimens usher in multiple medicolegal vicissitudes. These tribulations may carry potential and devastating repercussions to the wife, the husband, the donor, the relatives, and the physician. Unless both of the marital partners are deeply earnest and understand fully the possible and embarrassing medicolegal tangles the use of donor semen should be withheld. Beardsley¹² points out that the Supreme Court of Ontario,⁵⁹ in 1921, sustained a charge of adultery in a case wherein donor semen was used in artificial insemination. In addition to the charges of "adultery in the test tube" the child may be declared illegitimate and manifold legalities may surround any of the parties involved in the procedure. The donor may be named the correspondent in a divorce case by the husband. The donor may stoop to blackmail or become a contender in inheritance litigation should he learn the identity of the child. Adoption proceedings while assuring some degree of safety to the child provoke undesirable publicity which may frustrate the very purpose of the initial artificial insemination, to bring a child into a childless home.

The Bureau of Legal Medicine of the American Medical Association, in a letter to Beardsley,¹² advises that "no act is illegal unless prohibited by some law, either written or unwritten, and *society has formed no opinion and enacted no law regarding artificial insemination.*" (Italics ours.) Until the public opinion is molded, and safe and sane legal rules coupled with court opinions have removed the legalistic impediments from heterologous artificial insemination, it seems obvious that any system of affidavits, based upon embarrassing confidences, are worthless as protection for any of the parties concerned. Meanwhile we as physicians will do well to devote greater energy to more fundamental research in human fertility. We may be rewarded with findings which may obviate the use of donor specimens except in the most remote instances.

The Psychologic and Sociologic Aspects

The esthetic, psychologic, and moral reverberations resultant from the complex confidential relations between doctor and patient, doctor and semen donor, physician and child, may produce repercussions of singular unpleasantness to any one or all parties concerned. The basic unit of society is the family. The measuring stick of the family continues to be social propriety. The happy wife, contented through attaining a baby by means of homologous artificial insemination, may give voice to her joy and win approbation. But the woman, made pregnant by the use of donor semen, who even whispers out of turn, on a single occasion, be-

sembly line kind of medical treatment," although, in those selected and carefully studied cases the successful procedure may eventuate into "one of the most satisfying of medical experiences."

The author wishes to express his sincere thanks for the helpfulness and advice of Dr. Robert L. Dickinson, Dr. George W. Kosmak, and Dr. William H. Cary of New York City; Dr. Robert C. Cook and Dr. L. B. Tuckerman of Washington, D. C.; Dr. Alan F. Guttmacher of Baltimore, Md.; and Dr. G. W. Salisbury of Ithaca, New York.

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On the female side Langman and Burr⁶² report unique results in the electrometric timing of ovulation. In three patients, artificially inseminated, but once in a cycle, pregnancy supervened. In two other cases the evidence suggests that the patients did become pregnant following a single insemination (performed during a negative shift of the recorded cervical potential) but aborted soon after their first missed periods. Krohn and associates⁶³ described a new method for the quantitative determination of pregnanediol glucuronide and thereby suggest sources of error which may be eliminated in the chemical determination of ovulation.

Extensive experiments detailed above lead to but one conclusion. The need for heterologous artificial insemination is diminishing in direct proportion to our increasing knowledge about the male sex cells and the ovulatory mechanism in the female.

Summary of Conclusions

The status of artificial insemination as a means to overcome sterility in the barren couple, wherein the male is principally at fault, is a medical procedure valuable only as a final answer in certain carefully selected and thoroughly studied cases. This procedure offers no unusual promise as a panacea in the control of human male sterility, as is evidenced by a review of the available literature. With but one exception, Seymour and Koerner,²² those results obtained by resorting to artificial inseminations have been little more than mediocre. In the exception noted the careful reader will do well to review the unique findings with reasonable doubt, for this report, provocative of numerous inquiries as to its analytical reliability, contains numerous discrepancies and is at curious odds with the findings as reported by all others in the medical literature. In fact the principal reason for this critical review is to place on record a protest against publication of such extreme claims on the subject of human sterility until these are checked or verified.

More vigilance would preclude admittance of such undocumented "scientific" surveys to our medical periodicals and prevent thereby still greater perpetuation of error⁶⁵ in our "canned knowledge."⁶⁶ In these days when public opinion is considering socialized medicine with more than casual concern, it behooves medical writers and editors to back their facts with such incontrovertible proof as they can obtain because all too numerous lay writers stand ready to sell their interpretations of any medical paper, touching upon the dramatic, to the public via graphic and even lurid descriptive articles.

Artificial insemination may have its place in the medical armamentarium in the relief of sterility, although modern research in the physiology of human reproduction indicates that resort to it will become less and less necessary. The conservative physician will agree with Dr. Alan Guttmacher,⁶⁵ "artificial insemination must never be an as-

due to the action of the corpus luteum hormone upon the uterine muscle. Subsequent experiments²⁻⁷ upon the isolated uterus of nonpregnant and pregnant rabbits led him to conclude that the corpus luteum of this animal had, in addition to its action upon the endometrium, the function of decreasing spontaneous uterine activity and completely inhibiting its response to pituitrin during the time of the transportation, implantation and development of the fertilized ova.

That these deductions *might* be correct for the rabbit has been shown by Corner and Allen⁸ who succeeded in prolonging pregnancy beyond term in castrated rabbits by the administration of an active extract of swine's corpora lutea, and by Snyder⁹ who delayed the onset of labor in intact rabbits by producing ovulation and corpus luteum formation during late pregnancy through the injection of the gonadotrophic factor of human pregnancy urine. But this phenomenon may equally well depend upon the action of increased progesterone on the connection between fetus and mother. Robson and Illingworth,¹⁰ and Makepeace, Corner and Allen¹¹ confirmed Knaus' finding that natural and synthetic progesterone inhibited in vitro the reaction of the rabbit's uterus to pituitrin. Reynolds¹²⁻¹⁷ and Reynolds and Allen¹⁸ found the activity of the uterus of the living rabbit to be dependent upon the presence of estrogens without which in the castrated animal it became completely inactive, while on the other hand progesterone in adequate amounts produced complete uterine quiescence in castrates in which motility had been restored by large doses of estrogens. And moreover the response of the uterus to pituitrin or pitocin depended on the degree of its spontaneous activity at the time of administration, and was therefore greatest in the follicular phase of the cycle and absent in the luteal phase.

It therefore appears to be pretty generally agreed that in so far as the rabbit is concerned, progesterone, both in vitro and in vivo, diminishes the spontaneous contractions of the uterus and entirely prevents any response to pituitrin. Against this general agreement, however, Bell¹⁹ argued that the tension and distention inherent, respectively, in in vitro and in vivo experiments gave a false idea of its motility, and produced evidence that the "unloaded" rabbit uterus (i.e., freed from any artificial tension) was very active while under the influence of progesterone. And Siegmund²⁰⁻²² demonstrated that, while the motility of the rat uterus and its response to pituitrin were the same as those of the rabbit uterus during the follicular phase of the cycle, during the corpus luteum phase (or pseudopregnancy), pregnancy, labor, and the puerperium, the rat uterus responded strongly and characteristically to pituitrin. He therefore argued that the inhibitory action of progesterone upon the uterus of the pseudopregnant and pregnant rabbit was peculiar to that animal and the results of experiments made upon rabbits could not be applied indiscriminately to other animals.

In 1929 Knaus^{23, 24} extended his experiments to the human uterus, using as his material healthy women with regular twenty-eight to thirty-day cycles. In his original experiments, he filled the uterine cavity with lipiodol and, by means of a cervical cannula and the necessary connecting tubing and a mercury manometer, recorded the spontaneous contractions of the uterus upon a kymograph. Later he made use of a small, thin-walled rubber bag of about three to four cubic centimeters capacity which he introduced into the uterus, filled with sterile water and connected to a mercury manometer with water-filled pressure tubing.

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THE CONTRACTIONS OF THE HUMAN UTERUS DURING THE MENSTRUAL CYCLE

The Effect of Progesterone and Posterior Pituitary Extract Upon the Motility of the Human Uterus

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THE spontaneous contractions of the uterus and its response to drugs and hormones have been the subject of investigation for many years. It acquired a new interest with the work of Knaus whose far-reaching conclusions have given a new impetus to studies of uterine physiology. These have long since passed the stage of purely academic interest and have acquired a practical significance in modern therapy which warrants a brief critical examination of the work done and of the conclusions based upon it.

Knaus,¹ in 1926, drew attention to the fact that the uterus of the rabbit was insensitive to posterior pituitary extract up to the eighteenth day of pregnancy but from that time onward responded more and more strongly to this stimulus until, by the twenty-ninth day, premature labor could be induced, and suggested that this change was probably

immediate and marked increase in activity in the corpus luteum phase of the cycle.

Kurzrok, Miller and Coekerill,³² in 1936, while confirming Knaus' findings for the uterus of the rabbit, criticized the use of a bag for recording uterine contractions as it might induce expulsive efforts rather than true contractions. But in 1937 Kurzrok, Wiesbader, Mulinos and Watson³³ reported experiments on the uteri of nonpregnant women and concluded that the human myometrium contracted spontaneously and responded to pituitrin in both phases of the cycle but did both more strongly during the corpus luteum phase.

In 1938, Wilson and Kurzrok³⁴ described as a "functional myometrial cycle" the phenomena observed by Schultze, Robertson, Moir and Kurzrok and others. In the follicular phase the uterine contractions were small and frequent and their tone was high; in the luteal phase they were slower, much larger, and their tone lower. They felt that the myometrium took considerably longer to show the effects of progesterone than did the endometrium, and that the characteristic contractions of the follicle phase persisted into the corpus luteum phase while those of the corpus luteum persisted into menstruation. In a case of amenorrhea no spontaneous contractility or response to pituitrin was found, but they were able to reproduce the cycle of myometrial activity by administration of estradiol followed by progesterone. In anovulatory cycles, as would be expected, only contractions characteristic of the follicular phase were found. In dysmenorrhea they observed^{34, 35} no deviation from normal contractility, but their studies suggested that only those who ovulate and form a corpus luteum suffer from painful periods in the absence of recognized pathologic conditions of the pelvic organs. McLellan³⁶ also demonstrated the active spontaneous contractility and increased sensitivity of the nonpregnant human uterus to pituitrin during the luteal phase of the cycle. In 1940 Wilson and Kurzrok³⁷ showed that progesterone without estrin had little effect on the human uterine muscle, while testosterone produced an effect similar to that of estrogen and progesterone combined, including a characteristic response to pituitrin.

On the other hand Falls, Laekner and Krohn³⁸ claimed that one rabbit unit (Corner) of progesterone inhibited the puerperal human uterus and completely nullified its response to 1 c.e. of pituitrin. At the time Reynolds³⁹ criticized their results because they claimed to have obtained them within a few minutes after injection, although he later⁴⁵ accepted and quoted their claim. Krohn, Falls and Laekner⁴⁰ concluded that progesterone inhibited the contractions of the puerperal uterus, and again in 1937, Krohn, Laekner and Soskin⁴¹ concluded that progesterone decreased the motility of the nonpregnant, nonpuerperal human uterus.

As regards the isolated nonpregnant human uterus, Kurzrok, Miller, and Coekerill^{32, 42} found that of 350 strips studied, 90 per cent were stimulated by pituitrin regardless of the phase of the cycle and from the twentieth day of the cycle onward, the magnitude of the responses increased. On the other hand Adair and Hanzen⁴³ appeared to agree with Knaus that progesterone inhibited the response of the nonpregnant human uterus to pituitrin. They also concluded that early in pregnancy the human uterus in vitro is refractory to pituitrin and that pitressin acted more frequently and more powerfully than did pitocin on both the pregnant uterus at all stages of pregnancy and the nonpregnant uterus throughout the cycle. Moir²⁹ had previously pointed out that

His experiments indicated that during the follicular phase of the human cycle the uterus possessed a rhythmical spontaneous contractility and a characteristic rise in tone, amplitude and frequency of contractions following the intravenous injection of pituitrin. By the sixteenth to eighteenth day of the cycle its behavior changed entirely, and it now was almost or wholly inactive and failed completely to respond to pituitrin. This change in behavior he believed to be due to the inhibitory effect of progesterone upon the uterine muscle. That is to say, the human uterus resembled that of the rabbit in spontaneous motility and response to pituitrin in the follicular phase and in the inhibition of the latter during the corpus luteum phase; but unlike the "pseudopregnant" rabbit's uterus, which lost only its sensitivity to pituitrin while it retained its spontaneous contractility, the human uterus during the corpus luteum phase became almost or quite inactive.

Knaus' experiments have been repeated and modified by other observers. In 1930 Wittenbeek²⁵ confirmed his statement that in the presence of an active corpus luteum the human uterus lost its spontaneous contractility and response to pituitrin but found that the change might occur considerably earlier or later than Knaus had stated and was not invariably present.

Palmer, Christeas and Petrescu²⁶ agreed with Knaus that in the luteal phase of the cycle the human uterus was almost inert and the response to pituitrin was absent or feeble; this they corroborated by the evidence of luteal action seen in endometrial biopsies.

Schultze,²⁷ in 1931, quoted Joachimovitz²⁸ who had observed that the human uterus was more active premenstrually than postmenstrually. His own experiments resembled Knaus', but the results and the conclusions he drew therefrom are in sharp disagreement, for he found only a slight spontaneous motility and response to pituitary stimulation in the follicle phase, while from about midcycle onward a definite increase occurred in each until within twenty-four hours of the onset of menstruation. He was the first to point out that the amplitude and form of the contractions were characteristic of the phase of the cycle in which they were recorded and that the response to pituitrin increased progressively toward the end of the cycle and reached a maximum between the twentieth day and twenty-four hours before the onset of the next period.

In 1934 Moir,²⁹ using an intrauterine bag, found that the human uterus contracted throughout the cycle; in the first half the contractions were frequent, regular, and small, and in the second half they became stronger, less regular and increased in force until just before the onset of the period, when strong waves occurred at about three-minute intervals and reached a force which was in some cases as great as 100 mm. of mercury. During menstruation, the contractions were even stronger and came at two-minute intervals. In both phases pituitrin caused "spasmodic contractions."

Robertson,³⁰ in 1937, repeated Knaus' human experiments and confirmed his own results by endometrial biopsies done at the conclusion of each one. His findings were in agreement with those of Schultze and Moir, and the biopsies demonstrated the presence of a pro gravid endometrium at the time of greatest uterine activity and response to pituitrin. In 1939 he³¹ showed that emotional stimuli which produced no change in the pattern of spontaneous contractions in the follicle phase led to

sive therapeutic claims based upon its supposed inhibitory action, it seemed worth while to determine if possible whether such an effect did in fact exist. Ten patients, all but one of whom attended the Sterility Clinic of the Royal Victoria Hospital, made up the material for this study. Two had anovulatory cycles, two had no difficulty in becoming pregnant, but had repeatedly miscarried, five were apparently functionally sterile; that is, no demonstrable anatomic abnormality existed; and the tenth patient had had both ovaries removed at the age of 22 leaving the uterus intact. It was thought advisable since we wished to compare our results with those of Knaus to follow his technique as closely as possible. We accordingly secured from Graz balloons and cannula as described by him²⁴ and used a mercury manometer and kymograph as he had done. This method conforms very closely to that used by Moir,²⁹ Robertson,^{30, 31} and Kurzrok and others.^{32-35, 37} In addition we made endometrial biopsies after each experiment as Robertson, Kurzrok and others had done. To correlate the results obtained still more closely with the functional state of the ovaries, we studied the pregnanediol excretion in seven of the patients by the method described by Venning.⁴⁸ In some cases this study was carried out during several cycles, in others only during the cycle in which tracings were made. In one the assays were incomplete and in one no urine samples were obtained. The results obtained can best be stated by briefly examining the record of each patient separately.

CASE 1.—Mrs. F. C., aged 38 years, had a thyroidectomy for exophthalmic goiter in 1928. Menses 14 by 28 by 4 to 5. She had had amenorrhea for nearly one year at 23 years of age, had been married five and one-half years; and had had 3 miscarriages: first at twelve weeks (approximately); second at sixty-third day; third at seventy-first day. The basal metabolic rate was ± 0 .

Following her third abortion in March, 1939, pregnanediol assays showed regular ovulation with an unusually large pregnanediol excretion; biopsies showed the early changes in the progestational phase to be normal, but at the end of the cycle there were dilated glands with flattened epithelium and an apparent lack of secretion. Tracings were made on the eleventh, eighteenth, and twenty-fifth days of the cycle. The first showed small fairly regular contractions, and after 10 units of pituitrin their tone was slightly increased, their amplitude about doubled, and they became rather more regular. On the eighteenth day the spontaneous contractions were larger, slower, and less regular and some showed small ones superimposed on the larger; 10 units of pituitrin increased the tone and amplitude and the contractions became more regular; the effect was noticeable within four minutes and within twenty minutes the contractions became definitely painful. Biopsies showed a late progestational phase on the twenty-fifth day. Pregnanediol assays made on daily twenty-four-hour specimens of urine showed an excretion of 7.4 mg. on the eighteenth day and 5.7 mg. on the twenty-fifth day. These are considered to be evidence of the existence of a functionally active corpus luteum (see Figs. 1, 2, and 3).

as much as 10 units of pitocin had no effect on the nonpregnant uterus in vivo while pitressin had a strong effect leading to long-continued spasm of the muscle. Robson⁴⁴ found the same relation in excised strips of human uteri in early pregnancy, but showed that response to pitressin returned in late pregnancy. Bell¹⁹ showed that the uterus of the castrated rabbit did not respond to pitocin while under the effect of either estrogen or progesterone. And finally McLellan³⁶ claimed that pitressin and not pitocin was the factor in posterior lobe extracts which was responsible for their stimulus to uterine muscle and argued that the reaction to whole pituitary extracts and to preparations of pitocin was in fact due to the pitressin which they contained and from which they could not be entirely separated.

One of us (J. S. H.) some years ago studied the contractions of strips of human uterine muscle obtained at cesarean section at or near term and from uteri removed early in pregnancy for the purpose of therapeutic abortion and sterilization. In both early and late pregnancy there was very active spontaneous motility and a never-failing and quite typical response to pituitrin.

In his monograph on the *Physiology of the Uterus*,⁴⁵ Reynolds has reviewed an immense literature bearing upon his subject. In the main he supported Knaus' theory of progesterone's inhibitory action upon the myometrium and based his conclusions to this effect in the case of the human uterus upon rectal studies of its cyclical activity made by Dickinson.⁴⁶ He appears to have accepted Knaus' claims as proved and argues at length that Kurzrok and others who have disagreed with him must be in error in experimental methods or interpretation of data or in both. He did not, however, repeat Knaus' experiments upon the human uterus.

From the foregoing it will be seen that there is a difference of opinion concerning the effect of progesterone on the human uterus. Some authors support Knaus in the view that the uterus is spontaneously contractile and responds to pituitrin only in the follicle phase of the cycle, while in the presence of an active corpus luteum whether of the normal cycle or of pregnancy spontaneous motility and sensitivity to pituitrin cease. Others again support Schultze in the opposite view; namely, that there is a type or pattern of uterine contractions characteristic of the follicle phase and another characteristic of the corpus luteum phase, and pituitrin produces typical increases in frequency, amplitude, and tone in each, but in the corpus luteum phase both the pattern of the spontaneous activity and the effect of pituitrin upon it are much greater than in the follicle phase and increase steadily until the maximum is reached about the onset of menstruation or within the first hours of the period.

Personal Observations

In view of the conflict of opinion regarding the effect of progesterone on the myometrium of animals and of human beings and of the exten-

CASE 2.—Mrs. H. C., aged 22 years, menses 12 by 26 to 35 by 3 to 5, had been married one and one-half years. There had been no pregnancies. Preliminary studies of endometrial biopsies and pregnanediol excretion indicated the regular occurrence of ovulation and the formation of a corpus luteum; the luteal phase was of normal length as shown by pregnanediol output which lasted ten to twelve days and was about the average normal amount or perhaps a little less. The biopsies showed that the early progestational changes were normal, but the late progra-

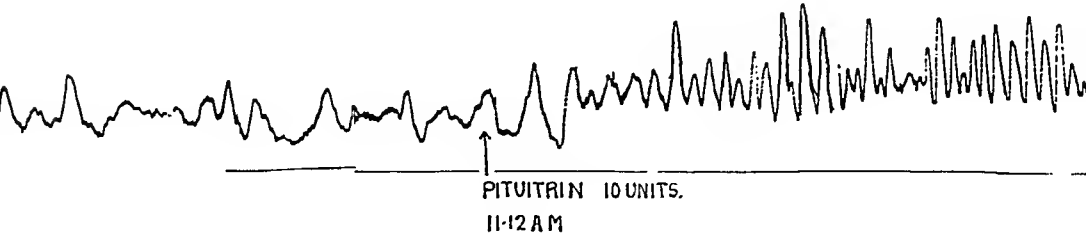


Fig. 4.—(Case 2.) The tracing on the twenty-fifth day of the cycle shows great spontaneous uterine contractility and response to pituitrin.



Fig. 5.—(Case 2.) The microphotograph shows the endometrium to be in the progestational phase.

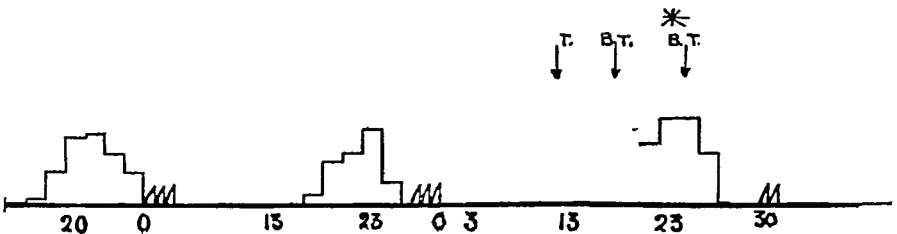


Fig. 6.—(Case 2.) The graph indicates the excretion of pregnanediol during three cycles.

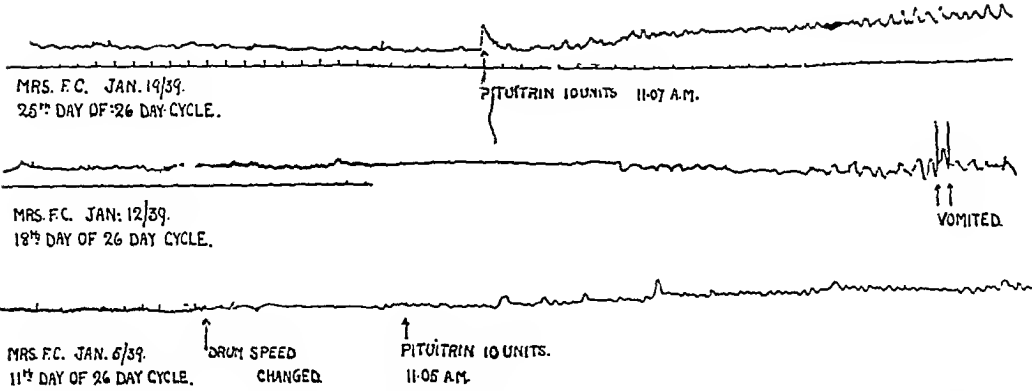


Fig. 1.—(Case 1.) The tracings show a progressive increase in spontaneous uterine activity and response to pituitrin throughout the cycle, approaching a maximum in the last day before menstruation.



Fig. 2.—(Case 1.) The biopsy shows a moderately deficient progesterational phase; note the dilated glands and the relative deficiency of secretion.

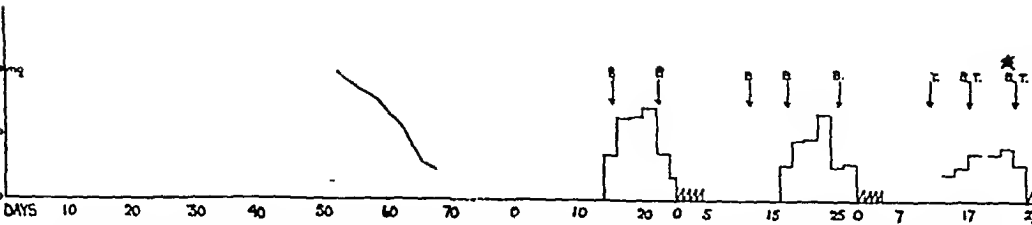


Fig. 3.—(Case 1.) The graph shows the excretion of pregnandiol in the two weeks preceeding the third abortion and during three cycles. (N. B. In all figures B indicates biopsy; T, tracing; and an asterisk the biopsy reproduced here.)

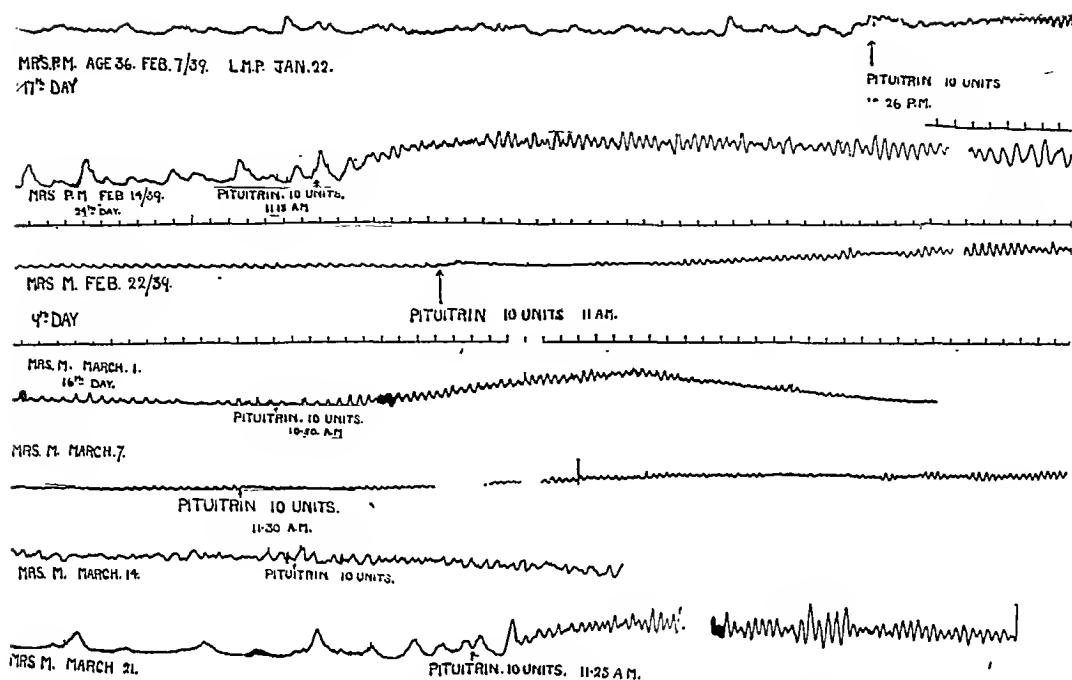


Fig. 7.—(Case 3.) The first tracing shows the somewhat irregular but powerful contractions of the uterus which characterize the early luteal phase; the second was taken a few hours after menstruation had begun and shows the increased activity and response to pituitrin described by Moir and others. The next three tracings are characteristic of the follicular phase of the cycle; and the sixth is incomplete (see text) but suggests strongly the effect of progesterone; and the seventh resembles closely the second which was taken during the first hours of menstruation.

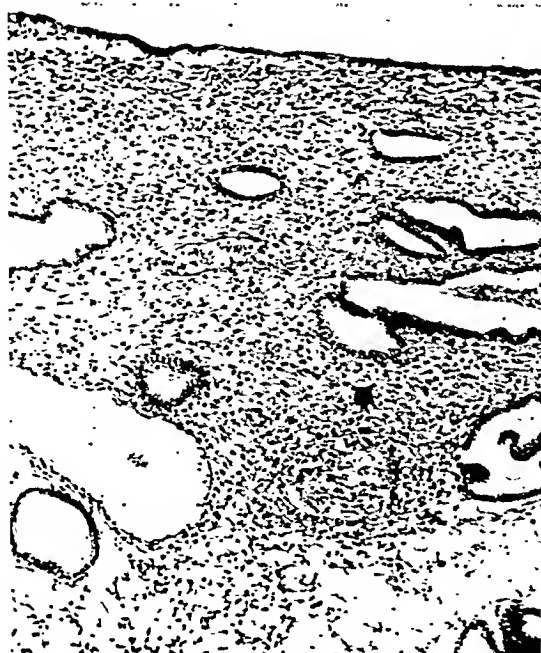


Fig. 8.—(Case 3.) The biopsy shows an abnormal late progestational phase; note the dilated glands, flattened epithelium, lack of secretion and deficiency of stromal development.

endometrium was characterized by dilated glands, flattened epithelium and deficient evidence of secretion. Tracings of uterine contractions were made on the eighteenth and the twenty-fifth day of the cycle. The first was of no value because of a defect in the apparatus. The second was marked by very large, slow, irregular contractions with small waves superimposed on many of them; 10 units of pituitrin intramuscularly produced at the end of three minutes a very marked rise in tone, amplitude and rate of contractions which soon took on the appearance of those recorded in the late first stage of a normal labor, and were felt as strong cramps, described as much worse than those of her menstrual periods. A biopsy at the end of the experiment showed an abnormal late progestational endometrium, the pregnanediol output for the day was 8.9 mg., and she menstruated five days later. These facts indicate the existence of a functionally active corpus luteum (see Figs. 4, 5, and 6).

CASE 3.—Mrs. P. M., aged 36 years, menses 11 by 27 to 28 by 5 to 6, without pain. At the age of 33 she had a full-term delivery; and the first abortion occurred Aug. 14, 1937, at about three months; second, May, 1938, was one week beyond the expected date of her period and she passed a uterine cast; third (observed by the authors), Dec. 1, 1938 on the seventy-first day.

Two tracings were made in one cycle and five in the next. The first was on the seventeenth day and the spontaneous contractions were rather large and irregular with smaller superimposed waves; 10 units of pituitrin intramuscularly produced a rapid rise in tone and the contractions became rapid and regular. On the twenty-fourth day the spontaneous contractions were much larger and pituitrin produced a similar but much greater effect. Biopsy on the seventeenth day yielded endometrium in the early progestational phase, and on the twenty-fourth day the tissue was from an abnormal late progestational phase.

On the ninth day of the next cycle the spontaneous contractions were small, fairly rapid and regular, and 10 units of pituitrin increased the tone, rate, and amplitude; the entire tracing, however, was unlike the previous two. On the sixteenth day the spontaneous contractions were like those of the ninth, but a little stronger and pituitrin produced a similar effect but the tone was more strongly effected. On the seventeenth, eighteenth, and nineteenth days bleeding occurred but was much less than a normal period. On the twenty-second day the contractions closely resembled those of the ninth day and pituitrin had a similar effect. Biopsies on each of these days produced sections of endometrium that definitely belonged to the proliferative phase and showed no evidence of any secretory activity whatever. On the twenty-ninth day there was difficulty with the apparatus and the first hour's tracings were of no use; at the end of the hour and before the apparatus was repaired, 10 units of pituitrin were administered by the patient's nurse. After repair had been effected the contractions resembled those seen on the seventeenth day of the previous cycle, but were smaller; a second 10 units of pituitrin intramuscularly one hour later produced little effect. On the thirty-sixth day the spontaneous contractions were large, slow, and irregular and 10 units of pituitrin intramuscularly produced the same rise in tone, amplitude, and rate of contractions seen on the twenty-fourth day of the previous cycle and were accompanied by cramps which reached their maximum intensity at the height of the contractions.

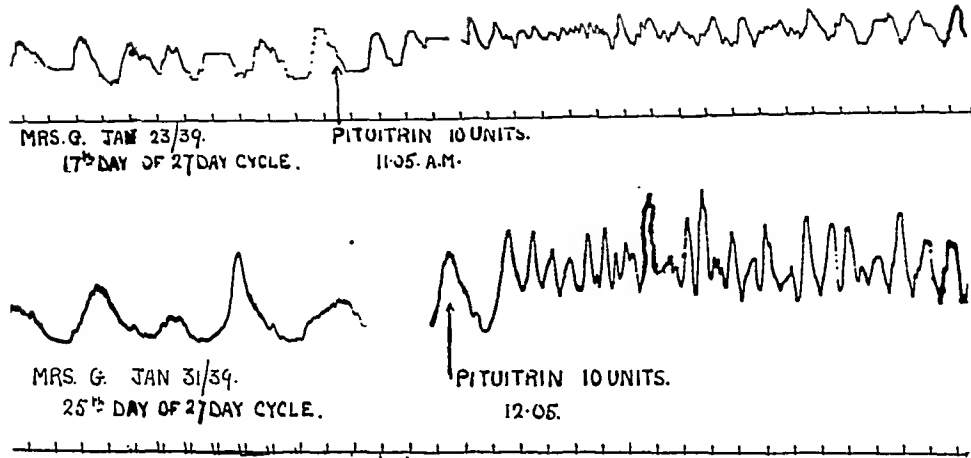


Fig. 10.—(Case 4.) The first tracing is characteristic of the early and the second of the late luteal phase of the cycle. Note the resemblance of the second tracing to Fig. 4.



Fig. 11.—(Case 4.) The biopsy shows the endometrium to be in the late progestational phase but somewhat deficient in its development.

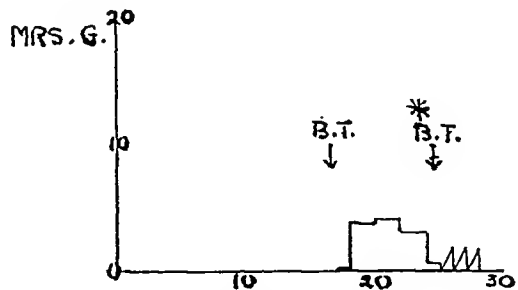


Fig. 12.—(Case 4.) The graph indicates the excretion of pregnanediol during the cycle.

Biopsies on the twenty-ninth and thirty-sixth days, respectively, showed a very early progestational change with some dilatation of glands, and an abnormal late progestational phase with considerable early decidual change in the stroma, and dilated glands with very flat epithelium and no evident secretion. Assays for pregnanediol were begun on the thirteenth day but none appeared until the twenty-ninth day when 1.9 mg. was excreted, and on the thirty-sixth day the secretion was 4.1 mg. Menstruation began on the thirty-eighth day. These data indicate a late ovulation followed by an active corpus luteum. The hemorrhage on the seventeenth to nineteenth days was probably the result of the biopsy and does not seem to indicate that the developing follicle had perished and been succeeded by a new one. A similar occurrence was noted in Mrs. A. P. (see Figs. 7, 8, and 9).

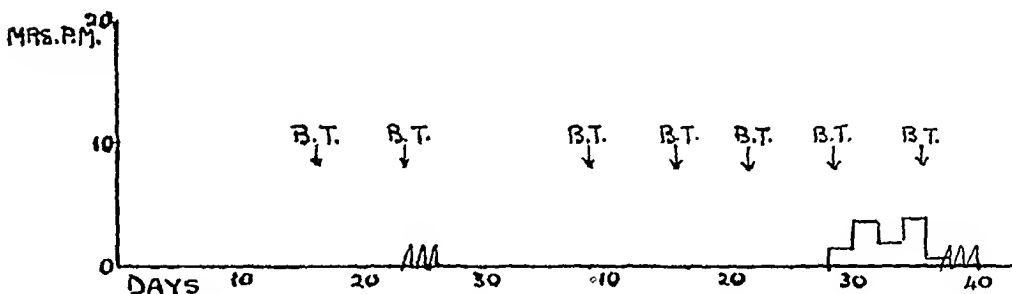


Fig. 9.—(Case 3.) The graph indicates the excretion of pregnanediol during the second cycle whose tracings appear in Fig. 7.

CASE 4.—Mrs. G., aged 26 years, menses 14⁺ by 28 by 3 to 4, had a history of subacute pelvic inflammation in 1937. Patient complained of sterility. Traeings were made on the 17th and 25th days of the cycle. On the seventeenth day, the spontaneous contractions were large and fairly regular with some smaller superimposed waves; after pituitrin there was a definite rise in tone, frequency, and regularity. On the twenty-fifth day, the spontaneous contractions were very slow and irregular, and after pituitrin there was an immediate rise in tone and frequency, and the contractions were now very like those seen at the same stage of the cycle in the second case. They were painful and described as much worse than a bad period. A biopsy on the seventeenth day showed epithelial nuclei lined up in the bases of the cells, in some of which there were a few basal vacuoles. This is taken to be the beginning of the progestational transformation and to indicate the action of progesterone on the endometrium. Pregnanediol appeared as a trace on the next day. The biopsy on the twenty-fifth day showed some flattening of glandular epithelium and deficiency of secretion, and there were early decidual changes in the stroma. This indicates a somewhat deficient progestational phase and with the finding of 0.9 mg. of pregnanediol shows the existence of a corpus luteum. Menstruation began two days later (see Figs. 10, 11, and 12).

CASE 5.—Mrs. A. P., aged 25 years, menses 12 by 28 by 5 to 6, had been married two and three-fourths years. She miscarried (?) in May, 1938, since then she had had premenstrual dysmenorrhea. In February, 1939, a biopsy on the thirteenth day of the cycle produced endometrium

in the proliferative phase; on the twentieth day there was normal early progestational change and on the twenty-eighth day there were marked decidual changes in the stroma, and the glands were dilated with flattened epithelium and little or no secretion in them, indicating the presence of a corpus luteum and an abnormal endometrial response.

In the next cycle, a tracing on the ninth day recorded rapid regular contractions and 10 units of pituitrin increased their tone and amplitude; the endometrium was in the proliferative phase. This experiment was followed by bleeding on the ninth, tenth, eleventh, and part of the twelfth days that resembled a period but was painless. On the sixteenth day the spontaneous contractions were smaller than on the ninth, rapid, and regular, and 10 units of pituitrin produced an immediate rise in tone and a later rise in amplitude. There was no biopsy done on this day and no assay for pregnanediol, but the contractions and response to pituitrin are of the pattern regularly seen in the follicle phase of the cycle. On the twenty-third day spontaneous contractions were large, irregular, and slow, and 10 units of pituitrin led to an immediate increase in frequency and greatly increased amplitude with complete relaxation. The biopsy showed a fairly late progestational phase with little decidual reaction. On the preceding day, pregnanediol excretion was 4 mg. She menstruated on the third day after the experiment. As she lived over ten miles from the hospital, urine assays were incomplete, but there is sufficient evidence of the existence of an active corpus luteum (see Figs. 13, 14, and 15).

CASE 6.—Mrs. Mc., aged 28 years, menses 12 by 10 to 21 by 11½, was married at the age of 13 years. The first pregnancy occurred at 14 years of age, but there had been none since. Tubes were patent. The husband's semen failed to show any spermatozoa.

This patient was observed throughout 5 cycles. In each biopsies indicated the presence of a corpus luteum, but the progestational phase of the endometrium in each was abnormal and the abnormality appeared to be present throughout the whole phase. Pregnanediol excretion was low and very irregular. In the last cycle studied, she received 1 mg. of estrone on the twenty-first, twenty-third, twenty-fifth, and twenty-seventh days. Two tracings during this time recorded small, rapid, regular contractions; in the first, pituitrin produced no change, and in the second, there was a rise in tone and amplitude. On the thirty-second day the urine contained 2.4 mg. of pregnanediol, the endometrium was of the midprogestational pattern but showed abnormal development suggestive of a deficiency in the function of the corpus luteum, and the contractions were large, irregular, and slow. Pituitrin produced a prompt rise in tone and frequency (see Figs. 16, 17, and 18).

CASE 7.—Mrs. J., aged 23 years, menses 13 by 28 to 30 by 3 to 4, cramps on first day, had been married ten months, but had not become pregnant.

On the eleventh day of the cycle, biopsy showed the endometrium to be in the proliferative phase. On the sixteenth day some glands showed early linear arrangement of nuclei with basal vacuoles and suggested the beginning of the progestational transformation. The tracings made on the same day at first consisted of small, rapid, and fairly regular contractions which later became larger and more irregular; 10 units of

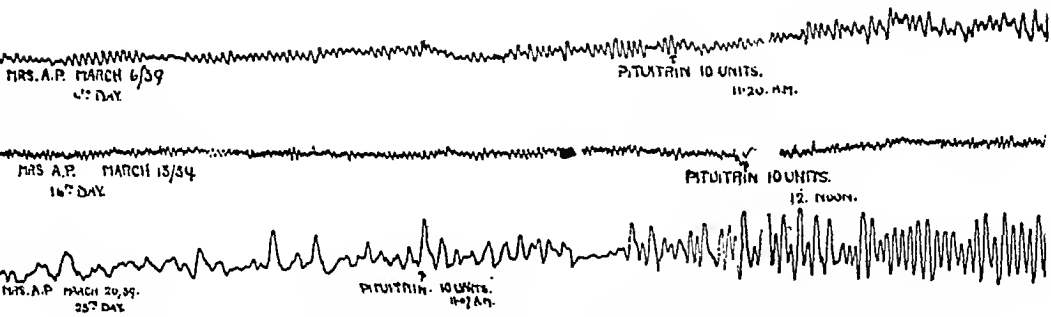


Fig. 13.—(Case 5.) The first tracing is of an active uterus in the follicular phase of the cycle; the second is also characteristic of the follicular phase, but the uterine activity is less than it was earlier in the cycle (see also fifth tracing in Fig. 7 and Figs. 16, 21, and 22). The third tracing is characteristic of the luteal phase of the cycle.

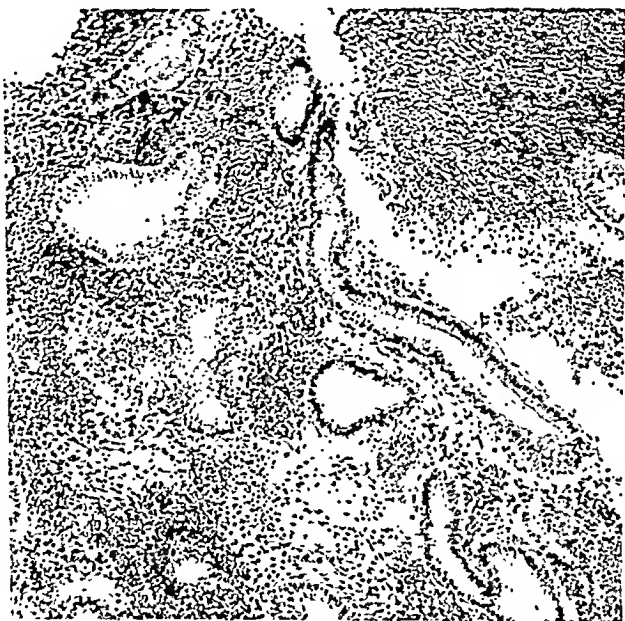


Fig. 14.—(Case 5.) The biopsy was taken on the twenty-third day of a twenty-eight-day cycle and shows the endometrium to be in the progestational phase, apparently corresponding fairly well to the stage of the cycle.

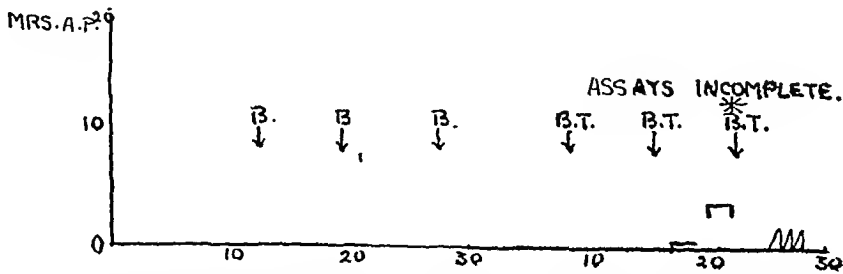


Fig. 15.—(Case 5.) The graph shows that there was no pregnanediol excreted when the second tracing was made; it appeared between 48 and 72 hours later, so this tracing was made very shortly before ovulation.

pituitrin produced considerable rise in tone and later in amplitude and greater regularity. No assays were made because she refused to go on with the investigation (see Figs. 19 and 20).

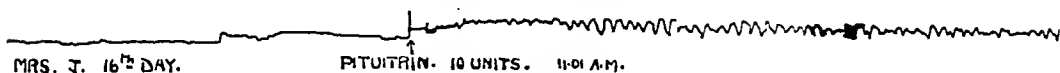


Fig. 19.—(Case 7.) The first part of this tracing is irregular and somewhat suggestive of the early luteal phase, and the response to pituitrin suggests the effect of progesterone.

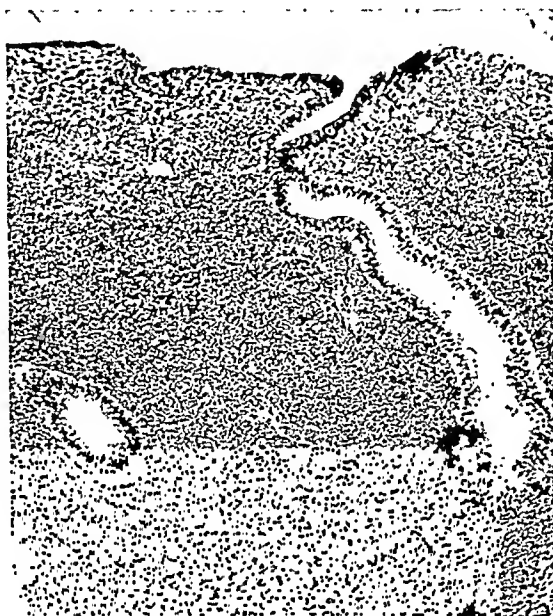


Fig. 20.—(Case 7.) The biopsy shows definite evidence of early progestational transformation. No assays were done.

CASE 8.—Miss S., aged 22 years, had had both ovaries removed in May, 1939, for bilateral cystomas; febrile convalescence. Pelvic examination before the experiment showed no pelvic mass, exudate, or tenderness.

She was admitted on July 6, 1939. Tracings showed small regular contractions resembling those of the follicle phase but of small amplitude. Pituitrin increased the tone and amplitude and considerably slowed the rate of contractions. *Biopsy*: small piece of very atrophic endometrium.

July 14, 1939: After 2 injections of 50,000 units each of estradiol benzoate (estroform) on the ninth and eleventh, tracing showed waves similar to those in the first tracing but smaller; 10 units of pituitrin slightly increased their rate and amplitude with very little effect on their tone. *Biopsy*: endometrium showed some development; glands were small and had a single layer of flattened cells; nuclei of stroma were fibrillar, naked, and widely separated by edema; the whole mucosa was very thin. The response to estrogen in the endometrium had been slight; this was true of the vaginal mucosa as well.

July 21, 1939: After further injection of 50,000 units of estradiol benzoate on the fourteenth, seventeenth, and nineteenth, spontaneous contractions were small and irregular; pituitrin 10 units produced a

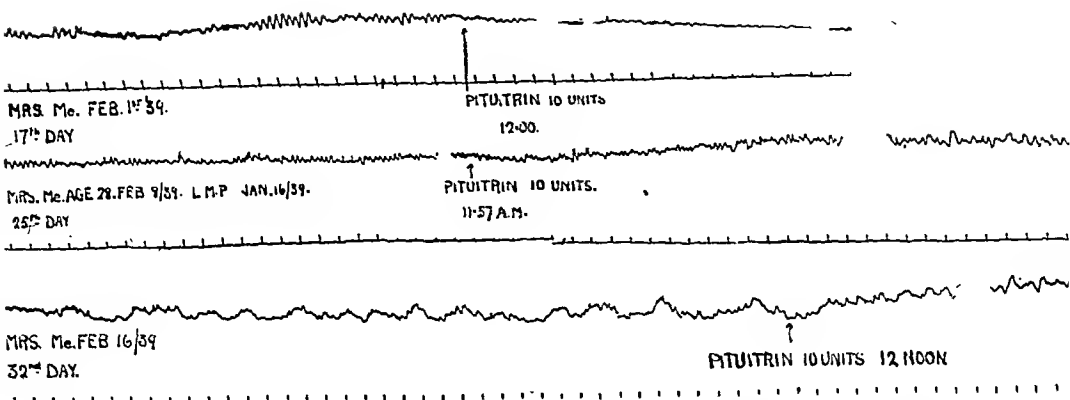


Fig. 16.—(Case 6.) The first tracings are characteristic of the follicular phase of the cycle. The third shows the definite effect of progesterone. All tracings were made in the last of five cycles studied (see Fig. 17).



Fig. 17.—(Case 6.) The biopsy shows a very poorly developed endometrium, but there is definite evidence of the effect of progesterone in the linear arrangement of the gland nuclei and the vacuoles of secretion at the base of the gland cells. Pregnandiol was excreted on the day of this biopsy and the third tracing in Fig. 16.

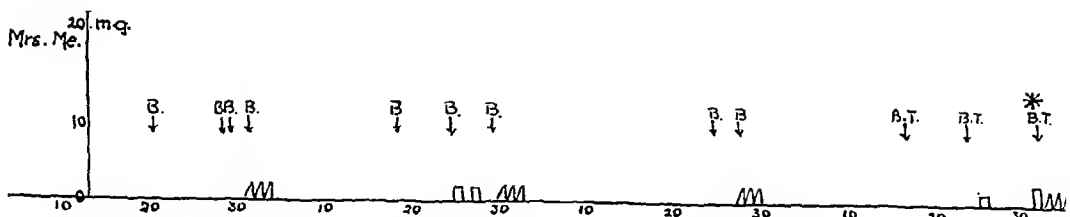


Fig. 18.—(Case 6.) The graph shows a very irregular excretion which occurred in only two of the five cycles studied.

CASE 10.—Mrs. P., aged 34 years, menses 14 by 25 to 30 by 4 to 5, complained of sterility.

On the tenth day of the cycle, uterine contractions were small and rather irregular, and 10 units of pituitrin produced only a rise in tone. On the nineteenth day spontaneous contractions were small, rapid, and regular, and 10 units of pituitrin produced no observable effect. On the twenty-sixth day spontaneous contractions were somewhat larger, rapid,

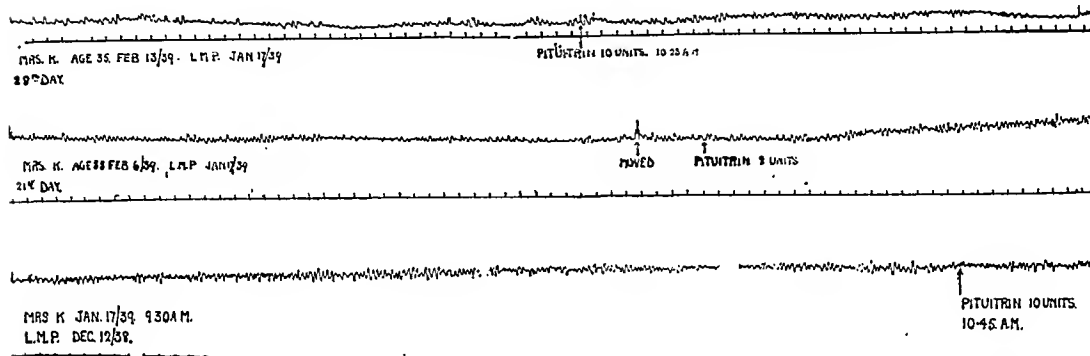


Fig. 22.—(Case 10.) All tracings were made during an anovulatory cycle (compare Figs. 7, 16, and 21).

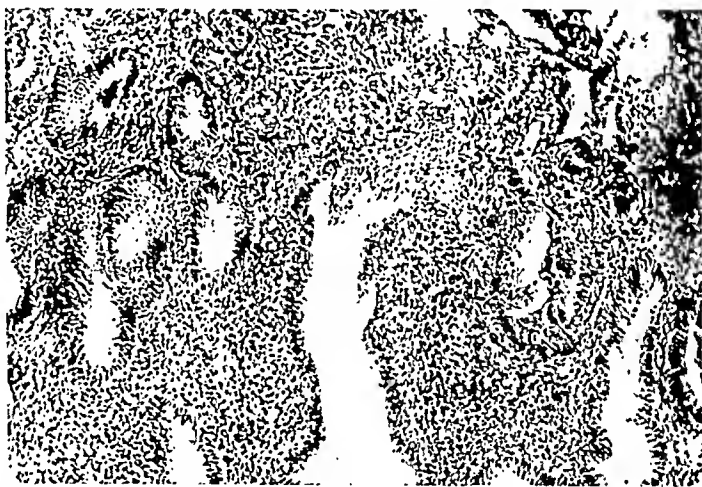


Fig. 23.—The biopsy shows endometrium in the proliferative (follicular) phase of the cycle. Assays in two cycles showed no excretion of pregnanediol.

and fairly regular, and 10 units of pituitrin produced a rise in tone and decrease in amplitude. Menstruation occurred on the thirty-ninth day of the cycle. Biopsies on the above days produced endometrium in the proliferative phase; no evidence of secretion or of progestational transformation could be seen. Assays for pregnanediol were done during two cycles but were negative throughout. These data indicate the occurrence of repeated anovulatory cycles (see Figs. 22 and 23).

rise in amplitude and frequency fairly characteristic of the follicle phase of the cycle. *Biopsy*: better developed endometrium; stroma cells shorter and plumper; glands partly pseudostratified and better developed; not entirely like normal late proliferative phase.

July 28, 1939: After further 50,000 units of estradiol benzoate on July 21 and 2,500 units (progynon benzoate) on July 24 and 26, combined on each of these two days with 10 mg. of progesterone, the spontaneous activity of the uterus had entirely changed; the contractions were now very large and slow with many small contractions superimposed on them; pituitrin appeared to increase the regularity and amplitude of the small contractions and tended to abolish the large slow waves in favor of the small. *Biopsy*: stroma more closely packed, nuclei plumper than on twenty-first; glands pseudostratified and some becoming quite tortuous, but showing no sign of secretion except that occasional glands suggested an early lining up of nuclei at their cell bases; this section was very like a very late proliferative phase (see Fig. 21).

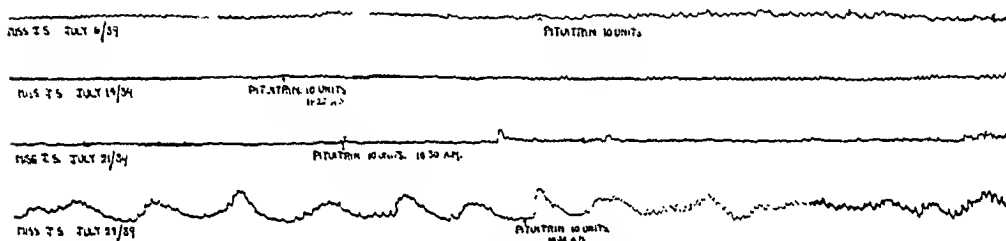


Fig. 21.—(Case 8.) The first tracing was taken two months after bilateral oophorectomy and before any estrogen therapy. The second and third followed large doses of estrogens (compare Figs. 7, 16, and 22). The fourth followed the combined injection of estrogen and progesterone.

CASE 9.—Mrs. K., aged 35 years, menses 18 by 2 to 4 months by 4 days, complained of sterility. Since marriage twelve years ago, menses occurred every four to eight months. Her last menstrual period occurred on Dec. 12, 1938; before this she was amenorrheic for eight months. The basal metabolic rate was -18 . She had been taking thyroid (B & W), gr. ii, b.i.d., since Nov. 29, 1938.

On Jan. 17, 1939, the thirty-seventh day of the cycle, uterine tracings recorded regular, rapid contractions of considerable size, and 10 units of pituitrin produced a slight rise in tone and later in amplitude. *Biopsy* showed the endometrium to be in the late proliferative phase. Menstruation began the next day and lasted for five days. On the twentieth day of the next cycle, contractions resembled those of the thirty-seventh day of the previous one but were smaller, and 10 units of pituitrin produced a gradual and prolonged rise in tone and amplitude. The endometrium was in the late proliferative phase. Following this she "spotted" a very little for four days. On the twenty-seventh day the spontaneous contractions and the effect of 10 units of pituitrin were very similar to those seen on the thirty-seventh and twentieth days of the previous cycles. The endometrium was again in the late proliferative phase, as it was once more on the thirty-ninth day. After this no further biopsies or tracings were made. No assays were done as neither biopsies nor tracings suggested the occurrence of ovulation or formation of a corpus luteum.

histologic changes in the glands and of pregnanediol in the urine were closely related to the change in pattern of uterine activity.

A fifth case was completely studied except that urinary assays were not done every day; the results obtained correspond to the foregoing in every way. A sixth case (Mrs. Me.), observed throughout several cycles, evidently ovulated in each, but pregnanediol was excreted very irregularly and in small amounts. Her tracings, however, conform to the pattern described for the two phases of the cycle including the increased spontaneous activity and response to pituitrin of the luteal phase.

In none of these six cases is there any suggestion that the myometrium responds more slowly to progesterone than does the endometrium as observed by Wilson and Kurczok.³⁴ On the contrary the change in pattern of motility was seen in all quite as soon as was the endometrial change characteristic of the effect of progesterone, and in one case it seemed to precede by twenty-four hours the appearance of pregnanediol in the urine. In all cases the response to pituitrin was seen within three or four minutes, unlike Moir's cases in which the changes occurred only twenty minutes after the injections. It may be that in his cases the injections were not given intramuscularly.

A seventh case in which no pregnanediol studies were made showed endometrial changes suggestive of the very earliest progestational change and the tracings and response to pituitrin resembled the pattern of the luteal phase and appeared to be quite distinct from that of the follicular phase.

In one case it was attempted to produce a cycle artificially. It is realized that this was not an ideal case for this purpose because of the foregoing postoperative pelvic inflammation. The tracings, however, indicate that the uterus retained its spontaneous contractility for a considerable time (two months at least), after bilateral oophorectomy. It seems curious that the spontaneous contractions should be smaller in the second and third experiments after very considerable doses of estradiol; however, a similar observation was made in the prolonged cycle of Mrs. P. M. and the more normal cycle (in length) of Mrs. A. P. The administration of estrogen should have been carried on at a much higher level along with the progesterone which, again, should have been given daily. As it was, bleeding occurred before the experiment was completed. It seems obvious, however, that coincident with the administration of progesterone there was a great change in the type of contractions which now became fairly characteristic of the corpus luteum phase of the cycle. The effect of pituitrin at this time was not entirely conclusive, but appeared to resemble that seen in the presence of a corpus luteum. This experiment, though not very satisfactory, indicates definitely the existence of great uterine activity and the presence of sensitivity to pituitrin after the administration of progesterone and sug-

Discussion

The records which we have presented include four cases in which one or more cycles were fully studied by means of biopsies, pregnanediol assays, and uterine tracings. In each there were found two patterns of uterine contractions: one which corresponded to the follicular phase of the cycle, and a second to the luteal phase. The first or follicular pattern was characterized by rather small, rapid, and fairly regular spontaneous contractions. On this pattern pituitrin, which in all our experiments was given in 10 unit doses deep in the gluteal muscles, produced a moderate rise in tone and amplitude, which was never striking and sometimes was very small. The second or luteal pattern was distinguished by the appearance of larger, slower, and less regular contractions than those previously seen, and frequently these waves had smaller waves not unlike those of the follicle phase superimposed upon them. As the luteal phase advanced, the pattern of the contractions was maintained, but there was a progressive increase in their amplitude. The effect of pituitrin, given as above, on this pattern of activity was to produce an almost tetanic contraction within three or four minutes followed by increasing relaxation between the individual contractions and a great rise in their tone, amplitude and frequency while at the same time the superimposed waves disappeared. This effect of pituitrin was obtained at all stages of the luteal phase but became progressively stronger as the end of the cycle was approached and reached a maximum during its last day or two and the first day of menstruation. At this time the contractions in three patients resembled in every way those recorded by the same method during the first stage of normal labor (see Figs. 4, 10, and 13). In one patient, on the twenty-fifth day, spontaneous contractions were painful and pituitrin made the pain "much worse than that of a period." There was considerable individual variation in the intensity of the uterine contractions during the luteal phase of the cycle and in response to pituitrin, but the pattern of activity was in each case characteristic, and after the first forty-eight hours following ovulation, unmistakable.

The following data have been accepted by us as evidence of the existence and function of a corpus luteum: (1) the nuclei of the gland cells of the endometrium line up in a single row at the bases of the cells and between them and the basement membrane vacuoles of secretion begin to appear; these are probably the earliest changes in the progestational transformation of the endometrium (Rock and Bartlett⁴⁹); (2) the appearance of decidual changes in the stroma and the characteristic tortuosity and "feathering" of the glands with the presence of secretion in their lumina distinguish the late progestational phase of the cycle; (3) the excretion of pregnanediol in the urine indicates the existence of a source of progesterone, which in the nonpregnant state is the corpus luteum (Venning⁴⁸). In our cases the appearance of the early

have been made concerning its value in the treatment of dysmenorrhea, afterpains, and particularly of threatened and habitual abortion. It may be said at once that experience and experimental evidence have both shown that it is of no value in dysmenorrhea or afterpains. It would be beside the point to discuss the merits of its use in the therapy of threatened and habitual abortion in this communication, but it should be pointed out that if it is of therapeutic value in these conditions it is not because of any inhibitory action upon the myometrium, but must rather depend upon its known function of preparing and maintaining the decidua by which it makes possible the establishment and maintenance of the necessary vital contact between the maternal and fetal organisms.

Summary

In each of four women with fairly normal ovarian and uterine function as shown by their ability to conceive, one or more cycles were fully studied; including pregnanediol assays, endometrial biopsies, and uterine tracings; a fifth was completely studied except that urinary assays were not done on every day; a sixth whose cycles were abnormal to the extent that she was unable to conceive was also studied and a seventh had tracings and biopsies done in one cycle but no pregnanediol assays were made. In each the uterus contracted more strongly and was much more greatly affected by pituitrin in the presence of the corpus luteum than during the follicle phase. An artificially produced cycle showed a similar increase in spontaneous activity and response to pituitrin after injection of 20 mg. of progesterone. Two cases of anovulatory cycles showed spontaneous activity and response to pituitrin characteristic of the follicle phase.

Conclusions

The uterus of the sexually mature woman is spontaneously active and responds to pituitrin throughout the entire cycle. Its spontaneous activity and sensitivity to pituitrin are greatest in the luteal phase; both reach their maximum just before the onset of menstruation or during its first day.

The weight of experimental evidence and of experience is against the claims made for the use of progesterone in treating dysmenorrhea and afterpains, and if it is of value in the therapy of abortion it must be because of its action in maintaining the decidua and so making possible the vital maternal-fetal connections.

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gests that the myometrium is affected by progesterone quite as early as is the endometrium.

Finally there were two cases of anovulatory cycles. In each of these the pattern of uterine motility was obviously that of the follicular phase and the response to pituitrin was also typical of this phase.

There are individual variations in the activity of human uteri, but these studies indicate that they all possess two types or patterns of motility, one characteristic of the follicular phase of the cycle and the other of its luteal phase. It might be argued from the one case whose ovaries had been removed that there may actually be an inherent contractile function of the uterine muscle which is acted upon first by estrogens to produce what we have called the follicular pattern and then by estrogens and progesterone in combination to produce the luteal pattern. Further studies of human castrates, however, would be necessary before this could be demonstrated. It is to be doubted if the study of tracings of the contractions of the uteri of amenorrheic individuals would throw much light on this point, since so many amenorrheic patients can be demonstrated to be excreting estrogens in their urine.

It is hard to say why Mrs. F. C. who excreted much more pregnanediol than did any of the other cases should possess a less active uterus than the others. This may be only an individual variation; on the other hand, the amount of pregnanediol excreted does not necessarily in all cases mirror the amount of progesterone secreted. Indeed the great excretion might indicate a failure of utilization of progesterone. At any rate Mrs. F. C. miscarried for the fourth time in fifteen months after these experiments; while Mrs. H. C. and Mrs. A. P. have had living children at term, the former not without repeated threats of miscarriage.

It may be argued that none of the six patients who were fairly completely studied presented normal endometria in their late gestational phases. This is true, and it is believed that this represents either a defect in the corpus luteum and a deficiency of the hormone produced by it, or a failure of the endometrium to respond adequately and normally to progesterone. But the pattern of myometrial activity and the response to pituitrin correspond to those seen in the luteal phase by Schultze, Robertson, Moir, and Kurzrok and others and that is the question under discussion. The relation of these deficiencies to diminished fertility is quite a different matter.

With such great uterine activity as is seen in some of these cases, it may well be that a partial ischemia is produced in the uterine wall by the powerful contractions which are equal in force in some instances to those recorded by exactly the same apparatus in the first stage of labor (unpublished observations of one of the authors) and may lead to dysmenorrhea as Moir²⁹ has suggested.

Based upon the belief that progesterone inhibits uterine contractions in the luteal phase of the cycle and in pregnancy, very important claims

WEIGHT GAIN IN PREGNANCY AND ITS RELATION TO WEIGHT OF INFANTS AND TO LENGTH OF LABOR

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THE weighing of patients has become an accepted part of routine prenatal care, and extended data are available regarding these weights. Undoubtedly the greatest value of this simple procedure is that excess weight gains, particularly rapid gains, serve as a warning signal for possible impending eclamptic disease. Upon this topic abundant observations have been made and nearly all authorities agree about the significance of the findings. In regard to the problem of the relation of weight gain to the size of the infant and the relation of weight gain to the length of labor, the literature is less adequate and the results are not in complete agreement. The purpose of this paper is two-fold: first, to summarize briefly the available literature and point out pertinent factors relating to these problems; and second, to introduce a new method of approach to their study and record the results of data collected.

Review of Literature

Most of the early studies regarding weight changes in pregnancy appear in the German literature. In the past two decades reports from American contributors have comprised most of the field. Gassner,¹ in 1862, seems to have been the first to record weight changes in pregnancy. In 1901 Prochownick² was the first to report the effect of diet upon size of infant and ease of delivery. Davis,³ in 1923, demonstrated a relation between weight gain in pregnancy and size of infant. The first to compare actual time of labor in patients who had dieted and those who had not was Friedman⁴ of Boston in 1926. A relation between weight gain in pregnancy and length of labor was demonstrated by Bingham⁵ in 1932. Paton,⁶ in 1903, appears to be the only worker to approach the problem from the standpoint of the experimental laboratory. Recently Stander and Pastore⁷ made a significant contribution to the problem by introducing to the American literature the concept of percentage weight gains.

Prochownick² believed he could effectively reduce infant size by diet. In 48 cases he achieved a reduction of birth weight in male infants to 11 per cent below what he considered a standard weight (3,333 Gm.), similarly 14 per cent in females. Paton⁶ fed 7 pregnant guinea pigs a normal diet and fed 4 pregnant pigs a poor diet. Those better fed produced more grams of offspring per gram of mother. He naively concludes maternal nourishment takes precedence over fetal requirements, which later experience seems to refute. From a study of 6,000

*Co-winner Taylor Instrument Company Prize awarded by the Rochester Academy of Medicine, 1943.

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over 10 pounds; of these 13 gained more than 24 pounds, the average weight gain for his series. Nine mothers gave birth to infants weighing less than 5 pounds and of these only 2 gained more than 24 pounds. An analytical study by Mellroy and Rodway,¹⁵ in 1937, of 1,000 women reports similar findings. In 704 primiparas the average baby weight increased slightly for each group of women, arranged according to 4-pound weight increases. They were able to plot a graph of these figures showing a straight line relation. For multiparas no such relationship could be demonstrated. When both groups were combined, the relationship held true only for those gaining the larger amounts. Hence the literature contains over 3,000 cases in which either the weight gain in pregnancy or the baby weights have been averaged and a relationship has been demonstrated between the two. The only observer unable to confirm these findings is Toombs.¹⁶ He analyzed 250 cases by dividing the mothers into two groups, those who gained less than 20 pounds and those who gained more than 20 pounds. He set these figures against those who had babies weighing under and over 7 pounds, respectively. He could find no relation between his various groups. It is to be noted that his selection of 7 pounds as the average baby weight may have vitiated his results.

The following have reported concerning the effects of diet on length of labor. Proehowniek,² in his ambitious venture, placed 62 patients who had previously difficult labors upon a detailed low caloric diet. He states that they had easier labors, less operative interference, and more live infants. Few obstetricians today would agree that his diet should be considered a part of the treatment for contracted pelvis. Hannah⁹ fails to support his statement: "The duration of labor is shortened several hours in patients where the weight gain is not greater than 15 pounds above the standard weight." Friedman's⁴ dieted primiparas had labors averaging six hours for the first stage, while the undieted group had first stage labors of a ten-hour average. The results for multiparas were much less striking, showing average first stages of five and one-half hours for the dieted group and six and three-quarters hours for the control group. The second stage of labor was not altered in either group. It is to be noted that all confinements in his group were relatively short regardless of diet. Slemons and Fagan¹² stated in 1927: "It is a matter of common experience that patients who take on weight excessively during pregnancy are prone to difficult labors." At the time of their statement common experience had not so recorded itself in the obstetric literature. Rueker's¹⁰ dieted primiparas had labors averaging twelve and one-half hours and his dieted multiparas, nine and one-half hours. Thirteen and one-half hours was the average length of labor for 296 other cases. He does not state parity or race of his control cases. In Bingham's⁵ large series he was able to demonstrate a relationship between amount of weight gained and length of labor. His patients gaining 1 to 10 pounds had labors averaging 10.4 hours for primiparas and six hours for multiparas. Those gaining over 31 pounds averaged 16.4 hours and 7.6 hours of labor for primiparas and multiparas, respectively. Those gaining 11 to 30 pounds had average labors between these extremes. Of Cumming's¹⁴ 1,000 cases, 23 per cent were operative deliveries. With patients gaining over 30 pounds, there were 45.8 per cent operative deliveries. By inference it is assumed the operative deliveries were the more difficult ones with prolonged labors. Evans¹⁷ divided his patients into those whose gain in weight averaged

infants and mothers in 1916, Smith⁸ states, "Bad nutrition slightly decreases the average weight of the full time baby at birth." It is well to note that Smith, twice badly misquoted in the American literature, makes no other statements. Hannah⁹ reported a series of 100 cases in 1923 and another hundred two years later. He concludes: "The weight of the baby is apparently not so great in patients whose gain in weight is limited." In neither paper does he record figures to support his contention. A small but clearly presented and suggestive series is reported by Friedman.⁴ He placed 24 primiparas and 30 multiparas, who were either overweight at the start of pregnancy or who gained more than 2 pounds per month, upon a low carbohydrate diet. These he compared with an equal number of undieted patients. The average weight of infants born to dieted primiparas was 6 pounds 15 ounces and that of the undieted primiparas, 7 pounds 5 ounces. For multiparas the average weights were 7 pounds 2 ounces and 7 pounds 15 ounces, respectively. Comparing 203 patients placed upon the Prochowick diet with 296 undieted mothers, Rueker¹⁰ found the average infant weight from dieted mothers to be 6 pounds 10 ounces and that of undieted mothers 6 pounds 15 ounces. Stating that the fetus gains most in weight during the last eight weeks of pregnancy, Perry¹¹ placed 20 patients on a diet during that period in an attempt to regulate fetal size. The babies of the dieted group averaged 6 pounds 14 ounces compared with 20 infants of non-dieted mothers which averaged 7 pounds 10 ounces. Following 10 patients through two pregnancies, using a diet during the second, the average baby weight of the first was 9 pounds 7 ounces and that of the second 7 pounds 5 ounces. • Thus results of diet influencing infant size have been reported by 5 observers and about 200 cases have been studied (excluding Smith's observation on 6,000 cases which was not a quantitative study). All conclude that diet limits the size of the offspring. •

A relation between weight gain of mother and weight of the infant has been demonstrated by several observers. The 150 patients reviewed by Davis³ had an average weight gain of 21 pounds and average baby weight of 7 pounds 14 ounces. Of these, 71 patients averaged a gain of 15.5 pounds and the average weight of babies born to them was 6 pounds 15 ounces. Twenty-one patients showed an average gain of 22.3 pounds, and the average weight of their offspring was 7 pounds 14 ounces. The remaining patients gained more than 25 pounds and had babies averaging 8 pounds. Slemons and Fagan¹² analyzed 500 cases in 1927, and noted that the weight of the infant was related to the weight gain of the mother. From an 11-pound average gain for those who had infants of 5 to 6 pounds in weight, the figures range to 26-pound average gain for those having babies of 10 pounds or over. Only one of their six groups shows no relation between infant weight and maternal weight gain. In an impressive series of 1,330 cases, Bingham⁵ averaged the weight of babies born to mothers who gained 1 to 10 pounds, 11 to 20 pounds, 21 to 30 pounds, and those gaining more than 31 pounds. • With primiparas a 3-ounce increase, at least, was noted in baby weights for each group as the mother's weight increased. Multiparas showed a less marked but still constant relation. • Hanley,¹³ in 1934, with 482 cases was able to demonstrate a similar increase in baby weights which were averaged to groups of mothers gaining in five-pound increments. • For some not apparent reason when the weight gains were compared to male and female infants separately, the relation did not hold so well. • Of 1,000 cases studied by Cummings,¹⁴ 17 mothers had babies weighing

parity, stature, climate, social status, and health. It would seem also that the size of the mother in addition to exerting an heredity effect on the size of the infant, would determine to some extent the amount of weight gained; for example, the larger women would gain the most weight. This is believed to be so by Gassner,¹ Zangemeister,²⁰ Lorenzens,²¹ Kemper,²² and Mahnert.²³ McIlroy and Rodway¹⁵ conclude from their study that the opposite is true. However, they base their statement on the fact that 4 out of the 5 patients in their series who failed to gain weight during pregnancy were large women weighing over 11 stone! Therefore, in charting amount of weight gained against the weight of the infant many observers may merely be dealing with two factors which vary according to the size of the patient. Hannah⁹ and Luikart¹⁹ believe consideration should be given to standard weights. Luikart believes tall, thin women may gain much without influencing the size of the fetus, but a similar gain in obese patients might result in a large infant.

Today the fetus, as concerns its metabolic needs, is generally regarded by obstetricians as a parasite. This being true it is not to be expected that drastic changes in fetal size should result from maternal diets. Average-sized infants are born to many mothers who failed to gain any weight during pregnancy. No reduction in the average size of infants was demonstrated in Germany during the last war when food was scarce, according to Williams,²⁴ Teel and Burke.²⁵ They believe only drastic starvation could effect a smaller size of infant. Adair,¹⁸ Slemmons and Fagan,¹² Friedman,⁴ and Harding and Van Wyck²⁶ agree. It should be noted that Friedman, although demonstrating a loose relationship between diet and size of infant, neither desired a general reduction of infant weight nor deemed it possible. Likewise, Slemmons and Fagan wisely concluded from their figures that an accurate determination of baby weight cannot be made, and the best to be hoped for is a prevention of excess fetal weight by proper diet. Because of the paramount part played by these variable factors, Holmes²⁷ emphatically states that no warranted scientific conclusions can be made regarding diet and the size of the infant. Harding and Van Wyck²⁶ emphasize a most important consideration in the relation of infant size to the conduct of labor: namely the size of the infant's skull. They point out that diet could not be expected to influence the size of the fetal skull. This obvious factor escapes mention by others. It is also equally apparent that in most deliveries it is the birth of the head which causes the most concern. They also note that excessive water retention in the mother would be expected to result in a heavier infant.

In determining the length of labor one obvious difficulty is determining when labor began. Frequently, especially in primiparas, labor will start with a few irregular pains to be followed by a lull of several hours. The accurate recording of the length of such labors may be difficult. Another factor, well known to obstetricians, is that some patients will have a well-dilated and taken-up cervix at the time of the first labor pain. Physiologically, these patients are certainly further along in labor than those whose pains begin with a firm, slightly dilated cervix; yet in recording the length of labor this factor is not accounted for. Aside from the increase in the size of the fetus, just why excess weight should predispose to longer labor is hard to ascertain. The earlier observers (Hannah,⁹ Slemmons and Fagan,¹² Hanley¹³) believed any excess weight gain meant fat in the maternal tissues, and Bingham⁵ states

less than 5 pounds per month and those who gained more. In a series of 211 cases, 86 primiparas gained less than this amount and had labors averaging seventeen hours; 14 primiparas gaining more, had labors averaging 18.2 hours. Of the multiparas, 97 gained less than 5 pounds per month and 14 gained more. The times of their labors were 11.4 and 11 hours, respectively. Two factors diminish the value of his observations: the liberal amount of 5 pounds per month as a dividing point for weight gains, and the fact that 52 of his patients had some evidence of pre-eclampsia. The literature then contains about 2,500 cases in which diet or weight gain is said to influence the length of labor.

In summary, there are considerable data which indicate that weight gain of the mother is related roughly to weight of the offspring and that diet may possibly play a modifying role in the regulation of the weight of the infant. Likewise, there is a moderate amount of evidence to indicate that a relation exists between length of labor and weight gain, and diet may exert some modifying effect upon the length of labor. It is now necessary to consider certain factors in these problems and to point out limits in the various methods of approach. The first is actually weighing the patient. Although different clothes may be worn at different weighings the same scale is usually employed throughout pregnancy, and it would appear that such data are sufficiently accurate to warrant conclusions. In speaking of weight gain it must be made clear that the scales may reflect two different and probably unrelated forms of weight. One is that due to the storage of excess fat in the tissues, the other to the retention of fluid. Accumulations of the former sort are usually gradual and do not disappear soon after delivery; while the latter may be stored very rapidly and are usually lost within ten days after delivery. Stander and Pastore⁷ estimate retained fluid to account for 16 per cent of weight increase in normal pregnancy. In the above diets when the restriction of salt was included with the diet it would be expected that fluid balance would be altered as well as the storage of fat.

In dealing with weight gain and the size of the infant, we encounter many variants. First, and most important, is the role of heredity. Many observers have expressed themselves upon this topic and their remarks appeal strongly to common sense. Because of the difficulty of an objective determination of the part played by heredity these proponents can offer no data, but proceed from inference. In a most delightful article Toombs¹⁶ champions this common sense attitude and emphasizes the influence of heredity. It is my contention that more wisdom is contained in his homely statements than that gleaned from partially understood masses of figures. He alludes to the fact of mule breeders matching the jackass with the mare; pointing out that these people have long known the jennet, regardless of diet, cannot foal the stallion's colt. Not only does the general size of the father's family play a part but that of the mother's as well. For although the mother be small, her family may be made up mostly of larger people and by the laws of heredity a return toward the norm for size would be expected in her children. Toombs¹⁶ concludes: "The size of the child at the time of delivery is determined by factors, in most instances, entirely beyond our control." Cummings,¹⁴ Adair,¹⁸ and Luikart¹⁹ agree with Toombs, but Cummings believes excess nourishment may increase the size of the infant. In addition to heredity, Hanley¹³ lists the following factors influencing weight gain as variables over which we have little control: race, age,

the differences are statistically not significant. Zangemeister's²⁰ studies revealed that season had no influence in altering weight gain. Hence we have been able to disregard age, body build, and season in the present study. Baby weight seems to vary slightly with different observers. Figures taken from the German literature and used by many as standard are 3,333 Gm. (7 pounds 6 ounces) for males and 3,250 Gm. (7 pounds 3 ounces) for females. In McIlroy and Rodway's study the figures were: infants of primiparous mothers, males 7 pounds 4 ounces, females 6 pounds 15 ounces; of multiparous mothers, males 7 pounds 6 ounces, females 7 pounds 5 ounces. Hanley's infants from primiparous mothers averaged 7 pounds 4 ounces, and from multiparous mothers 7 pounds 8 ounces. Cummings' cases averaged 7 pounds 7 ounces. We have not classified our infants according to sex, feeling that in 500 cases about an equal number would be of each sex, and that it would not materially affect the result. We may not be justified in making this assumption. Since we have selected only primiparas, the slightly heavier infants born to multiparas need not concern us here.

Procedure

For this study we have taken data obtained from the case records of 500 primiparas delivered at the Boston Lying-in Hospital within the past three years. Only normal patients, having normal deliveries and normal living infants, have been selected. None of the mothers had any pre-existing disease which was detected by routine medical history and physical examination, nor was any disease noted during the ensuing course of pregnancy. Thus we have excluded all such diseases as diabetes, tuberculosis, heart disease, renal disease, hyperthyroidism, and any other disease which might be expected to influence the weight gain in pregnancy. None of the patients was considered to have pre-eclampsia or eclampsia. We have used data from patients who showed a moderate amount of pitting edema, but have excluded those in which the edema was recorded as being very marked. None of the patients who had manifest edema had any albuminuria, hypertension, or symptoms of pre-eclampsia. When excess weight gain was not accompanied by any other abnormality, such cases were included. Those who lost weight during pregnancy, and those who continued to have vomiting beyond the third month were not included. All cases with abnormally shaped or borderline pelvis were excluded. When rupture of the membranes was premature or not followed shortly by labor pains, these cases were not used. The onset of labor was spontaneous, the presentations were all vertices, and aside from the use of low forceps no operative obstetric procedures were used. Occipitoposterior positions were included unless rotation was delayed enough to demand manipulative procedures. Pituitrin was given to only a few cases late in labor which were not progressing. All cases included in the study delivered within twenty days of the expected date of confinement. All patients used in the study were seen six months prior to delivery at one of the Boston Lying-in prenatal clinics and were followed regularly during pregnancy.

that diet reduces the amount of fat in the pelvis. Many have expressed the opinion that the muscles of the perineum have less elasticity if they contain much fat, and it has been suggested that the uterine musculature may behave similarly. Rucker¹⁰ believes that diet exerts a beneficial effect upon the uterus and allows the cervix to dilate more rapidly. By the prevention of overdistention of the uterus by regulating infant size, Friedman⁴ believes the uterus contracts more effectively. Fluid retention is thought by some to result in edematous muscle tissue which contracts poorly. It is clearly seen that these statements are mostly conjecture and difficult of objective proof. In reporting the beneficial effects of diet on patients who have had previously difficult labors mention of the parity of patients compared has been neglected by some previous observers (Prochownik,² Rucker,¹⁰ Davis,³ Friedman,⁴ Perry¹¹). It would be manifestly unfair to compare the type of labor of primiparas with that of multiparas. The duration of pregnancy is another factor which is not frequently recorded and accounted for in the conclusions drawn.

Personal Observations

From a consideration of the above factors influencing weight gain, size of the infant, and length of labor, it was felt a more fruitful approach to these problems could be used. It was decided to relate weight gain to the original weight of the patient and to do likewise with the problem of infant weight. It is hoped by this method to give a truer conception of the role played by weight gain in affecting the size of the infant and the length of labor; and in so doing to avoid some of the errors of previous workers.

Before such a study can be undertaken, certain basic data regarding weight gain in pregnancy must be used. In respect to this factor due credit should be given to the following workers who have established certain facts.

Siddall and Maek²⁸ have recorded the average weight gain for the last sixteen weeks of pregnancy to be 15.7 pounds. They have also recorded average weight gain for each of the four weeks between twenty-four and forty weeks. These they found to be 4.4, 3.9, 2.0, 2.1, 2.0, and 1.3 pounds, respectively. Cummings¹⁴ did the same for 1,000 cases followed from early in pregnancy. His cases showed an average total gain of 24 pounds (10.9 kilo). The gains by months were 0, 1, 1, 4, 4, 5, 5, 3, and 3 pounds, respectively. Stander and Pastore⁷ presented graphs showing the average gain per week in terms of percentage weights. Their 3,000 cases averaged weight gains of 24.1 per cent or 30.6 pounds (13.9 kilo). He points out that there is little or no gain during the first six weeks. It is because of Cummings' and Stander and Pastore's⁷ compilations that we are able to use a weight six months prior to delivery as about equal to the prepregnant weight. By using methods of statistical analysis Bray²⁰ has shown that parity, age, and body build do not significantly alter the amount of weight gained during pregnancy. The older patients, as best shown by Mellroy and Rodway,¹⁵ do show a very slight tendency to gain less weight, and this holds true to some extent for multiparas also. Hanley's¹³ primiparas averaged 22 pounds 6 ounces weight gain and the multiparas 21 pounds 3 ounces. But

perhaps best shown when the weight gain is expressed as a percentage weight. The correlation coefficients for these two graphs are calculated as 0.11 for weight gain and 0.19 for percentage weight. The graphs relating weight gain by the various two-month periods show no evidence of relation between them and the length of labor. Accordingly only one correlation coefficient was calculated for this group, and it was 0.06 for the percentage gain in the two months before delivery.

In attempting to ascertain if there is any linear relation between the size of the infant and the length of labor we have plotted two graphs. One expresses infant weight in pounds, the other in terms of percentage weight. There appears to be no relation whatever, and the calculated correlation coefficient of -0.003 for percentage weight of infant bears this out.

It was next attempted to determine whether the larger women gained the most weight and had the larger infants, and if the weight of the women bore any relation to the length of labor. The graphs indicate some tendency for the heavier women to gain more weight. For this graph the correlation coefficient is calculated to be 0.40. There is a very slight tendency for the larger women to have larger infants. This is not plainly seen in the graph, but the correlation coefficient we have calculated for the graph is plus 0.23. The graph plotted for weight of mothers against the length of labor gives no indication of any relationship.

As a control we have plotted the weight of the infants against the number of days from the expected date of confinement when delivery actually occurred. It was felt necessary to do this to eliminate any possibility that the term of pregnancy was altering the amount of weight gained or the weight of the infant. As seen in a graph* there is no evidence that this factor is altering our results. Since we have shown weight gain to be related to infant weight, it was not thought necessary to check the weight gain by such a graph.

As a matter of interest to compare with other workers we have calculated averages for our series. The average weight gain was 22.9 pounds, or 18.2 per cent of the mother's weight at three months of the pregnancy. These figures are slightly lower than those of Stander and Pastore which include the whole duration of pregnancy. The average infant weight was 7 pounds 4 ounces. Expressed as a percentage weight related to the mother's weight this is 5.8 per cent. The average length of labor was fifteen hours. The 500 women averaged 125 pounds six months before delivery and 148 pounds at delivery.

Comment

By the use of this method it is indicated that a relationship between weight gain and infant weight for our series of 500 cases is present. When this relationship is expressed as a linear correlation coefficient, it is seen that it is only moderately significant. A correlation of 0.5 indicates that a linear relationship is present, but it indicates only a trend when applied to large numbers of cases.³⁰ Thus we may state that there is a trend for infant weight to increase with an increase of weight gain in pregnancy; but it would not be wise to attempt to apply this tendency

*For lack of space the graph is not included here.

From the case records we obtained the following data: Weight of patient six, four, and two months before delivery, and at delivery; weight of infant; hours of labor, and the number of days the actual delivery varied from the calculated date of confinement. The same scales were used for the six, four, and two months before delivery weights. In most instances the weight at term is from a weighing upon admission to the hospital for delivery. In some instances where this is not recorded we have used a weight from the clinic record which was within a week of the hospital delivery. We have used calendar and not lunar months; and the weight taken from the clinic record for various months is within a week of that exact period. Duration of labor is calculated from the onset of regular recurring pains to the birth of the infant.

From this data we have calculated the following: total weight gain for the six months' period, weight gain for each of the two months' intervals preceding delivery, percentage weight gains for the six months' period and for each of the two months' periods, and percentage weight of the infant. The percentage weights are calculated by dividing the weight gained by the weight of the patient six months prior to delivery. Similarly infant weight expressed as a percentage is obtained by dividing the weight of the infant by the weight of the mother six months prior to delivery. As stated above we are assuming that this weight six months before term is practically equivalent to the prepregnant weight of the patient.

We have attempted to relate these various factors by plotting them upon scatter graphs. The graphs are in two major groups. One deals with the problem of weight gain and infant weight and the other with the problem of weight gain and length of labor. We have then calculated linear correlation coefficients for eight of the more significant graphs. For this calculation we have used the formula shown in Table I.

TABLE I

POUNDS GAINED	AVERAGE LENGTH OF LABOR HOURS	BABY WEIGHT
5-9	8.5	7.7
10-14	14.6	6.9
15-19	15.3	7.1
20-24	15.1	7.4
25-29	17.0	7.7
30-34	16.4	7.6
35-39	16.5	7.9
40-44	17.7	8.2
45-49	23.0	7.7
50-54	23.0	8.7
55-59	13.0	7.2

Results

* The only graph, which by its arrangement plainly shows an evident linear relation between the two factors plotted, is that of percentage weight gain related to percentage infant weight. The calculated linear correlation coefficient for these data is 0.53. The graph relating actual weight gain to infant weight shows a less clear relationship and the corresponding linear correlation coefficient is 0.28. •

The graphs attempting to relate weight gain with length of labor indicate no evident linear relation. What little relation is present, is

Conclusions

1. A tendency is shown for increasing weight gains in pregnancy to be associated with infants of heavier weights.
2. There appears to be only a very slight tendency for women who gain increasing amounts of weight to have longer labors.
3. The increase in infant weight associated with increased weight gain appears to have no influence upon the duration of labor.
4. There appears to be some tendency for the larger women to gain more weight during pregnancy and slight tendency for them to give birth to larger infants.
5. The use of percentage weight in expressing weight gain in pregnancy and infant weight is a useful method in dealing with the problems of weight gain and weight of the infant.

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to individual cases, and prediction of infant weight from a particular weight gain would not be possible.

From our cases there appears to be no linear relation between weight gain and length of labor. In the face of correlation coefficients of 0.1 and 0.2 for these factors, it would not be wise to state that a trend exists. Likewise, there appears to be no linear relation between time of labor and the weight gained in the various two-month periods of pregnancy. From the results of this study there seems to be no indication to propose another theory as to how weight gain influences labor.

If the tendency for larger infants to be born to those mothers gaining more weight is to have any practical significance for obstetrics, it would be that the larger infants are associated with longer labors. Our graphs and correlation coefficients indicate that such is not the case at all. Hence, from our study it cannot be stated that reducing the weight of the infants should result in easier or shorter labors.

Our graphs and correlation coefficients indicate that larger women tend to gain more weight and have a slight tendency for larger infants. Hence when previous authors have drawn up tables relating weight gain and size of infant they are probably dealing with two factors which depend to some extent upon a third, namely the size of the mother. That the size of the mother is not more closely related to infant size suggests that possibly the size of the father may play a significant role in determining the size of the infant. A study to determine this relationship is contemplated.

So that our results might be comparable to those of others, we have constructed tables in the manner of Bingham, Slemons and Fagan, Hanley, McIlroy and Rodway. Although not as striking as some of their tables they indicate a trend. Perhaps they would be more striking if larger groups were used. It is our contention that these tables are deceptive in that they give the impression of a good relationship between the factors expressed. It is felt that scatter graphs give a truer picture of what the relationship means when applied to individual cases and that the linear correlation coefficient gives one a better idea of the reliability of this relationship. From the studies it is felt that the use of percentage weights in expressing weight gain and infant weight is a valuable method to use in dealing with the above problem.

Summary

A review of the literature regarding the problems of the relation of weight gain in pregnancy to weight of offspring and length of labor is presented and the results of such literature are evaluated.

A study of 500 normal primiparas is presented in which data obtained are applied to the above problems. Percentage weights have been employed, graphs have been constructed and linear correlation coefficients calculated.

patients were seen once a week, and instructed to bring in twenty-four-hour urines at every visit. The urine volumes were measured as a check on the fluid intake; the urinary excretion of chloride was determined (Volhard's method⁶) as a check on the salt intake; and the creatinine excretion was measured (Folin's method⁶) as a check on the completeness of urine collection. The patients were usually seen on Mondays, because we felt that the less conscientious patients were more likely to break their diets for the American Sunday dinner. If the salt excretion were found to be low, it was presumed that the patient had adhered to the diet throughout the week.

These checks just described turned up an amazingly high incidence of dishonesty and falsehood, which was often remedied for the remaining weeks by showing the patient wherein she was caught. If one may generalize from our experience, it would seem that any study of dietary restrictions in out-patients must be buttressed by some objective check upon the patients' solemn asseverations that the diet has been followed.

Results

In analyzing our data, we have transferred a number of patients from Groups B and C into Group A, because their twenty-four-hour urines consistently showed salt contents of more than 5 Gm., and volumes inconsistent with the fluid intake which had been advised. If this is not fully justified, the effect might be to diminish somewhat the incidence of toxemia in the control (A) group. In 57 cases, we have no observations on the twenty-four-hour urines; 34 of these patients were in the control Group A. In the 23 remaining cases, some patients were uncooperative and some delivered prematurely. All patients whose twenty-four-hour excretion of salt was consistently less than 5 Gm. have been included as satisfactory B's or C's.

TABLE I. THE INCIDENCE OF PRE-ECLAMPSIA UNDER DIFFERENT DIETARY REGIMES

GROUP	A. CONTROLS	B. SALT AND FLUID RESTRICTION	C. SALT RESTRICTION, FORCED FLUIDS
Cases	89	85	63
Incidence of toxemia, per cent	22.5	23.5	7.9
Incidence of toxemia, including borderline cases, per cent*	25.9	29.4	14.3

*Borderline cases: *Group A*, 3 cases, 1 with an ante-partum rise in blood pressure which spontaneously subsided, and 2 cases with systolic or diastolic elevations alone. *Group B*, 9 cases, 1 with transitory ante-partum rise in blood pressure, 1 with an intra-partum rise, 2 with post-partum rises, and 5 with either systolic or diastolic rises alone. *Group C*, 5 patients, 2 with transitory ante-partum rise, 1 with post-partum rise, and 2 with systolic or diastolic rises alone.

While these patients are not strictly normal, they will not be included as toxemias in the subsequent tables.

The data shown in Table I indicate that patients under both salt and water restriction (Group B) had the same incidence of pre-eclampsia as did the controls, while the Group C patients had an incidence of pre-eclampsia of only about one-third that found in the other groups. While this is not in accord with what we had anticipated, we believe that the results can be rationalized. But first we shall analyze our data further, to see whether there has perhaps been a chance selection of favorable cases for Group C. This analysis is based upon our pre-

A STUDY OF SALT RESTRICTION AND OF FLUID INTAKE IN PROPHYLAXIS AGAINST PRE-ECLAMPSIA IN PATIENTS WITH WATER RETENTION

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THE prophylaxis and treatment of pre-eclampsia are almost purely symptomatic, chiefly because the fundamental nature of the disease is unknown. The measures taken have been widely varied, accordingly as one symptom or another has been emphasized, and as these symptoms have been variously interpreted. Today the prevailing opinion seems to be that water retention is at least a significant factor in the development of pre-eclampsia. For this reason it has become routine in many clinics to combat edema. As a means to this end, dietary salt is restricted by most clinicians, but there is a wide divergence of opinion as to whether water intake should be restricted, increased, or ignored. Extremes of practice are seen in the sharp limitation of fluid intake recommended by Arnold and Fay (the "Temple treatment"),¹ and in the forcing of fluids as practiced especially in the midwest (de Alvarez²). Since this difference of opinion and practice is so wide spread, and is to be found even among the three services in our own hospital, we have attempted to make a roughly quantitative study of the question.

We³⁻⁵ have previously described measurements of extracellular water in late pregnancy, and shown that about 20 per cent of clinically normal patients with abnormally large proportions of water will develop the pre-eclamptic syndrome. Thus the determination enables one to select potential pre-eclamptics, although many of the patients so selected do not later manifest hypertension and proteinuria.

Material

The present study deals with 237 patients having excessive water as found between the thirty-second and thirty-sixth weeks of pregnancy; these patients were selected from 1,388 cases in whom extracellular water was measured. These 237 patients were followed in a special clinic, and as they first came in they were assigned in rotation to one of three groups, viz: (A) Controls; no dietary restrictions were imposed. (B) Patient was given a 1,200 caloric, 2 Gm. salt diet and fluids were restricted to 1,000 ml. per day. (C) Patient was given the same 1,200 caloric, 2 Gm. salt diet, but told to force fluids. (At the outset of the study, patients were put into either Group A or Group B.) All

TABLE III. THE RELATION BETWEEN THE HIGHEST OBSERVED SYSTOLIC BLOOD PRESSURE AND THE SUBSEQUENT DEVELOPMENT OF PRE-ECLAMPSIA

<i>Maximal systolic pressure</i>						
GROUP	LESS THAN 120 MM. HG		121 TO 130		MORE THAN 131	
	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
A	31	6.5	38	31.6	18	38.9
B	22	4.5	27	14.8	34	44.1
C	20	0.0	31	3.2	10	40.0
Totals	73	4.1	96	17.7	62	41.9
<i>Proportion of patients in each category</i>						
A	35.7		43.6		20.7	
B	26.5		32.5		41.0	
C	32.8		50.8		16.4	

Note the chance selection of unfavorable cases in Group B, while Groups A and C are comparable

tially (but not wholly) accounts for their lack of response to prophylaxis shown in Table I.

3. *Highest Diastolic Pressure Before the Measurement of Extracellular Water.*—The effect of the maximal diastolic pressure upon the incidence of pre-eclampsia is very similar to the effect of the maximal systolic. This is to be expected, since the patients showing elevations in one usually also show elevations in the other. Table IV indicates that the Group C patients in all ranges of diastolic pressure have a much lower incidence of pre-eclampsia than do patients in Groups A and B. Again, there is a concentration of unfavorable cases in Group B.

TABLE IV. THE RELATION BETWEEN THE HIGHEST OBSERVED DIASTOLIC BLOOD PRESSURE AND THE DEVELOPMENT OF PRE-ECLAMPSIA

<i>Maximal diastolic pressure</i>								
GROUP	LESS THAN 75 MM. HG		76-80		81-85		MORE THAN 86	
	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
A	23	8.7	38	21.1	10	20.0	18	50.0
B	19	10.5	17	11.8	16	6.3	29	51.7
C	13	0.0	27	0.0	4	25.0	18	22.2
Totals	55	7.3	82	12.2	30	13.3	65	43.1
<i>Proportion of patients in each category</i>								
A	25.9		42.7		11.2		20.2	
B	23.5		21.0		19.8		35.7	
C	21.0		43.5		6.5		29.0	

4. *The Maximal Rate of Weight Gain Prior to the Measurement of Extracellular Water.*—Since rapid weight gain has received so much attention as being of significance in developing pre-eclampsia, we are including our data here. In the present series, rapid weight gain seemed to bear no relation to the subsequent appearance of the pre-eclamptic syndrome. (All of our patients had occult or occasionally frank edema as shown by the extracellular water measurements.) As Table V shows, the Group C patients again showed the best response to prophylaxis against pre-eclampsia. The three groups are comparable so far as rapidity of weight gain is concerned. (The data in Table V

vious findings⁴ that certain factors markedly augment the danger of pre-eclampsia in patients with excessive extracellular water. Unfortunately we do not have enough cases in some categories to warrant statistically sound conclusions.

Factors Conceivably Making for Chance Selection of Unfavorable Cases in Any One Group

1. *Degree of Abnormality in Water Retention.*—The greater the degree of increase in water retention the greater is the likelihood of pre-eclampsia developing. This trend holds for patients in Groups A, B, and C, but the patients in Group C have a lower incidence of pre-eclampsia (Table II). The proportions of patients from Groups A, B,

TABLE II. THE RELATION BETWEEN DEGREE OF WATER RETENTION AND THE INCIDENCE OF TOXEMIA

GROUP	Degree of water retention							
	+		++		+++		++++	
	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
A	51	17.6	20	25.0	9	11.1	9	55.5
B	50	24.0	20	25.0	8	12.5	7	28.6
C	38	2.6	14	7.2	4	25.0	7	28.6
Totals	139	15.8	54	20.4	21	14.3	23	39.1
Proportion of patients in each category								
A	57.3		22.5		10.1		10.1	
B	58.8		23.5		9.4		8.3	
C	60.3		22.2		6.4		11.1	

Note that Groups A, B and C are strictly comparable as regards degree of water abnormality

and C are very nearly the same when they are subdivided on the basis of degree in water abnormality. So far as degree of water retention is concerned, then, there has been no selection of favorable cases for Group C.

2. *Highest Systolic Blood Pressure Before Measurement of Extracellular Water.*—We have previously reported that the incidence of pre-eclampsia increases markedly when excessive water is found in conjunction with (1) higher levels of usual blood pressure, or (2) marked variability of blood pressure, or (3) higher maximal blood pressures at any time in pregnancy (which combines the first 2 factors). Table III demonstrates that the higher the maximal blood pressure (at any time in pregnancy and while the patient is still "normal"), the greater is the incidence of subsequently developing pre-eclampsia.

From the data in Table III, it appears that the dietary regimes of both Groups B and C were quite ineffective in preventing toxemia if the patient had ever shown a blood pressure exceeding 130 mm. Hg. However, in patients with lower maximal blood pressures there was a definite reduction in the incidence of toxemia in both Groups B and C, with the C group showing considerably better results.

The patients in Groups A and C are comparable so far as maximal systolic pressures go, since nearly the same proportions of each fall in each blood pressure range (Table III). In Group B, however, there is a concentration of unfavorable cases, in that many (41 per cent) had shown maximal systolic pressures greater than 130 mm. Hg. This par-

TABLE VII. THE RELATION BETWEEN BODY WEIGHT AND THE INCIDENCE OF PRE-ECLAMPSIA

GROUP	BODY WEIGHT LESS THAN 180 POUNDS		BODY WEIGHT MORE THAN 180 POUNDS		PROPORTION OF PATIENTS WITH BODY WEIGHT GREATER THAN 180 POUNDS
	CASES	% TOXIC	CASES	% TOXIC	PER CENT
A	73	17.8	16	43.8	17.9
B	55	18.2	30	33.3	35.3
C	42	7.1	21	9.5	33.3
Totals	170	15.3	67	28.4	28.3

7. *Parity and History of Toxemia.*—The incidence of toxemia is slightly higher in primiparas than in multiparas, and among multiparas is much higher in those patients giving a history of previous toxemia. Table VIII indicates that Groups B and C are closely comparable with each other, and not greatly different from Group A, when they are broken down in terms of parity and history. In a large proportion of cases in each group the history is not known definitely, but in all such cases, no record suggestive of previous toxemia appears in the charts. In all subdivisions of Table VIII, the Group C patients show the lowest incidence of toxemia.

TABLE VIII. THE RELATION BETWEEN PARITY (AND HISTORY OF TOXEMIA) AND THE INCIDENCE OF PRE-ECLAMPSIA

GROUP	PRIMIPARAS		MULTIPARAS					
			HISTORY OF TOXEMIA		NO HISTORY OF TOXEMIA		HISTORY UNCERTAIN*	
	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
A	20	25.9	6	50.0	17	5.9	39	23.1
B	27	20.0	9	33.3	18	27.8	38	21.1
C	14	14.3	6	33.3	14	0.0	29	3.4
Totals	61	21.3	21	38.1	49	12.3	106	17.0
<i>Proportion of patients in each category</i>								
A	30.3		6.8		19.1		43.8	
B	23.5		10.6		21.2		44.7	
C	22.2		9.6		22.2		46.0	

*Most histories probably negative.

Incidence of toxemia in all multiparas, 18.2 per cent.

Recapitulation of Analyses Bearing on Fairness of Allocation of Cases to Groups A, B, and C

In the foregoing tables, we have shown that the difference in response to the different prophylactic regimes probably cannot be attributed to the fortuitous selection of favorable cases for any one group. Every table shows that at least 2 groups are comparable with each other, and usually all three groups are similar. From the standpoint of the factors analyzed, a concentration of unfavorable cases was found first in one group, and then in each of the others as the factors were successively analyzed. The one really serious deviation from homogeneity among

TABLE V. THE RELATION BETWEEN THE MAXIMAL RATE OF WEIGHT GAIN AT ANY TIME IN PREGNANCY AND THE INCIDENCE OF PRE-ECLAMPSIA

GROUP	MAXIMAL GAIN LESS THAN 6 LB./MO.		MAXIMAL GAIN MORE THAN 6 LB./MO.	
	CASES	% TOXIC	CASES	% TOXIC
A	61	21.3	27	29.7
B	53	24.5	31	22.6
C	40	7.5	21	9.5
Totals	154	18.8	79	21.5
<i>Proportion of patients in each category</i>				
A	69.3		30.7	
B	63.1		36.9	
C	65.6		34.4	

have been condensed from a more detailed analysis in which the rate of weight gain was broken down into categories of 2 pound increments.)

5. *Duration of Water Abnormality.*—Since water retention usually precedes the rise in blood pressure in developing pre-eclampsia,⁴ it seems possible that the patients who begin to accumulate excessive water in the last weeks of pregnancy may deliver before the toxemic process becomes full-blown. We have, therefore, looked for an effect of duration of water retention upon the incidence of toxemia.

Longer periods of water retention are associated with a rising incidence of toxemia. In comparing Groups A, B, and C, we find that Group C uniformly shows a lower incidence of pre-eclampsia. Also Group C shows a concentration of unfavorable cases, in spite of which the toxemia incidence remains low for the whole group (Table VI).

TABLE VI. THE RELATION BETWEEN DURATION OF EXCESSIVE WATER AND THE INCIDENCE OF PRE-ECLAMPSIA

GROUP	<i>Interval from test to delivery</i>									
	LESS THAN 2 WEEKS		2 TO 4		4 TO 6		6 TO 8		MORE THAN 8 WEEKS	
	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
A	14	21.4	21	14.3	31	19.4	11	27.3	12	41.7
B	11	0.0	23	26.1	29	27.6	10	20.0	12	33.3
C	2	0.0	11	0.0	21	9.5	15	13.3	14	7.1
Totals	27	11.1	55	16.4	81	19.8	36	19.4	38	26.3
<i>Proportion of patients in each category</i>										
A	15.7		23.6		34.9		12.3		13.5	
B	13.0		27.1		34.1		11.8		14.0	
C	3.2		17.5		33.3		23.8		22.2	

6. *Body Weight.*—Patients with excessive extracellular water and weighing more than 180 pounds have a higher incidence of pre-eclampsia than do the lighter-weight patients. (There is no regular trend discernible when weights of less than 180 pounds are plotted against the incidence of pre-eclampsia.) When our patients are divided on the basis of weight (Table VII), it is found that the Group C patients show the lowest incidence of toxemia in any weight group. As regards weight distribution, Groups B and C are closely comparable, while Group A contains a relatively high proportion of lighter patients who are more favorable risks.

since the water loss in nearly all cases was considerably greater than the weight loss.)

Eighteen patients lost more than 1,500 ml. of extracellular water (12 in Group B and 6 in Group C). Two of these (in Group B) developed pre-eclampsia, giving an incidence of 11.1 per cent as compared with the 27.8 per cent incidence in patients who had gained water. Because of the few cases available for analysis, there are 23 chances in 100 that even this difference arises from a sampling error.

Finally, reduction of extracellular water to normal values seems to have no effect upon the incidence of pre-eclampsia. A total of 65 patients was found to have excessive water at the thirty-second week of pregnancy. In 20 of these cases, the water was reduced to normal values, but 20.0 per cent developed pre-eclampsia in spite of the normal proportions of water. Of the 45 patients whose extracellular water remained abnormally high (although occasionally reduced from the initial level), 24.4 per cent developed pre-eclampsia.

If any conclusion can be drawn from these data, it would seem that the beneficial effects of the dietary regimes in toxemia prophylaxis may not depend upon the reduction of occult extracellular edema per se. The results of the treatment seem not in accord with the rationale. It may be, of course, that 65 cases analyzed do not fairly represent the whole series of 237 patients.

Discussion

Why the symptomatic treatment of edema in late pregnancy should prevent the later appearance of hypertension and the rest of the pre-eclamptic syndrome is unknown, at least to us. But statistically, it seems that dietary prophylaxis against toxemia is effective in many patients who might otherwise develop pre-eclampsia. Insofar as we have broken down our data, the control and experimental groups are comparable.

Clinical observations bear out the statistical evidence that salt restriction does sometimes prevent toxemia. We felt that we had caught several patients at the very brink of toxemia, and reversed the morbid process. Such patients (all with occult edema) had shown a blood pressure creeping into the upper limits of normal, and had complained of a bloated sensation and of not feeling so well as usual. After a week or two on restricted salt, either with limited or forced fluids, the blood pressure often dropped 15 or 20 mm., a rapid weight loss had occurred, the patient felt much better, and looked better. (The majority of blood pressure changes defy reliable analysis because too much emphasis would be put on single readings. However, in at least 14 cases the drop from recent average systolic pressures exceeded 16 mm. Hg.)

The diet which we gave these patients is, of course, low in calories (1,200). The protein content is 84 Gm., and the vitamin content is somewhat low. (The estimated vitamin content of the diet is as follows: A = 3,500 I.U., B₁ = 1.6 mg., C = 188 mg., G = 1.8 mg. The estimated daily requirements are A = 9,000 I.U., B₁ = 2.0 mg., C = 100 mg., G = 1-2 mg.) It has been assumed that the salt restriction is the effective factor, chiefly from the a priori reasoning that sodium

the groups was on the basis of the maximal systolic blood pressure observed at any time in the pregnancy. In this respect there was a concentration of unfavorable cases in Group B, which predisposed to a higher incidence of toxemia.

In general, it may be said that proved salt restriction seemed to reduce the incidence of pre-eclampsia in clinically normal patients who had occult edema. The patients who simultaneously increased their fluid intake had a lower toxemia incidence than did those who restricted both fluid and salt intake. This superior performance in patients on unlimited fluids cannot, so far as we have analyzed the situation, be attributed wholly to a concentration of favorable cases in that group.

TABLE IX. THE RELATION BETWEEN WEIGHT CHANGE, WATER CHANGE AND THE INCIDENCE OF PRE-ECLAMPSIA

GROUP:		A		B		C		TOTALS	
		CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC	CASES	% TOXIC
Gain in weight		58	25.9	39	30.8	33	12.1	130	23.8
Loss in weight	Less than 2 pounds	11	27.3	15	20.0	17	5.9	43	16.1
	More than 2 pounds*	7	0.0	29	13.8	10	0.0	46	8.7
Gain of water		15	33.3	11	27.3	10	20.0	36	27.8
Loss of water†		3	33.3	16	25.0	10	0.0	29	17.2

*Average weight loss 5.3 pounds, range 2¼ to 12½ pounds.

†Fifteen patients lost extracellular water while gaining weight.

Changes in Weight and in Extracellular Water Under Salt Restriction, and Their Relation to the Development of Pre-Eclampsia

The data in Table IX show that for all patients the incidence of toxemia dropped as the effect of the diet on body weight became more marked. Losses of weight under salt restriction might be presumed to represent in part losses of extracellular water, because restriction of sodium intake should lead to a depletion of body sodium which in turn causes an equivalent loss in extracellular water, either out of the body or into the cells. (This is, of course, the rationale of the salt restriction in treating edema.)

However, when we compare the incidences of pre-eclampsia in patients who lost water (17.2 per cent) with that in patients who gained water (27.8 per cent), there seems to be no significant difference. (Calculation of chi square from a fourfold table shows 45 chances in 100 that the difference could rise from sampling alone.) Unfortunately, the checks on extracellular water after 3 or more weeks on the dietary regimes were made in only 65 cases. Of the 29 patients losing extracellular water, 15 simultaneously gained weight. This leaves only 14 patients who lost both weight and extracellular water. One of these, in Group B, developed preeclampsia in spite of a 9 pound loss in weight; however, her loss of extracellular water was only 500 ml., still leaving an abnormally high proportion of water. (This is an unusual finding,

tients might permit cellular rehydration and, over a period of days and weeks, also permit an increase in the volume of extracellular water in some patients. If the beneficial effect of the diet depended upon cellular rehydration, then changes in volume of extracellular water need not be closely correlated with the effectiveness of the diet in preventing toxemia. The superior performance of the patients who forced fluids might depend upon a greater degree of cellular rehydration, although another explanation (diuresis) is possible. Restriction of fluids along with salt would tend to slow down or prevent cellular rehydration.

If cellular rehydration is the key to effective toxemia prophylaxis, it is hard to see why the incidence of toxemia decreases as greater losses in body weight are induced (Table IX). In short, the apparent discrepancy between the effects of weight change and of extracellular water change upon the incidence of toxemia leaves us in a quandary. The confusion is worse confounded by the finding that when patients do lose both water and weight, they lose much more water than the weight loss can account for. Having nothing better to offer than feeble speculation, we shall leave it at that.

Normally the body does not hold appreciable quantities of water, extracellularly, without retaining an equivalent amount of electrolyte to maintain isotonicity. Unless the pregnant woman developing pre-eclampsia deviates from normal in this regard, high fluid intakes should be harmless so long as the electrolyte, chiefly sodium, intake is restricted. Furthermore, an increased fluid intake might even be beneficial for the best diuretic is water and with diuresis some extracellular electrolyte tends to be swept out through the kidneys. Such loss of electrolyte (NaCl chiefly) would be accompanied by the loss of extracellular water previously retained. Forcing fluids, together with effective salt restriction might be expected to rehydrate the cells if they are dehydrated, and to reduce the volume of extracellular water.

In toxemia prophylaxis, our patients who forced fluids showed the lowest incidence of toxemia. Since we have not made any observations on patients with the more advanced pre-eclamptic syndrome, we can say nothing as to the advisability of forcing fluids in the treatment of toxemia.

Summary and Conclusions

Clinically normal patients who had begun to retain excessive quantities of extracellular water in late pregnancy showed a 20 per cent incidence of subsequent pre-eclampsia.

In the present study, 237 such patients were assigned in rotation to 3 groups: (A) Controls, (B) restricted salt and fluid intake, and (C) restricted salt and forced fluid intake.

Detailed analysis showed that the groups were fairly comparable.

limitation should reduce extracellular water, and the demonstration that it does so in nephritis, nephrosis, cardiac decompensation, and in demineralization experiments.⁷ Also Harding and Van Wyck,⁸ by varying different components of the diet, showed that it was salt restriction which benefited patients with toxemia. Strauss⁹ writes, "Many methods of treatment of 'toxemia' which have met with more or less success, have knowingly or unknowingly been measures to eliminate water retention." He then shows this to be true for 9 different therapeutic measures, including salt restriction. Conversely, substantiating evidence is seen in the rapid weight gain and exacerbation of pre-eclamptic signs and symptoms following salt administration (Harding and Van Wyck,⁸ Strauss⁹).

It is, then, puzzling to find that reduction of extracellular water, even to normal values, seems to have no beneficial effect in toxemia prophylaxis. Some of the possible explanations might include: (1) The permeability of some cells may change enough to admit the thiocyanate used in measuring extracellular water. This would make the determinations unreliable. (2) The 65 cases analyzed may not be representative of the whole series of 237 patients. (3) Intracellular hydration or dehydration may be an important factor which is altered by salt restriction. Evaluation of this factor is very difficult with the present means of investigation.

In connection with the third possibility just mentioned, it is interesting to compare the water loss with the weight loss, although there are only 14 patients who lost both water and weight under salt restriction. In all but 2 cases, the water loss was greater than could be accounted for by the weight loss, and in 9 of the 14 patients the weight of water lost was more than twice the loss in body weight. In an additional 15 patients there was a loss of extracellular water while the patients were gaining in weight. This suggests that extracellular water may shift into the cells when salt is restricted. In previous papers,³⁻⁵ we have conjectured that in the last weeks of normal pregnancy there may be a shift of intracellular water out into the extracellular space. In developing toxemia this shift may be exaggerated. McPhail¹⁰ believes that a central feature of pre-eclampsia is cell dehydration in the presence of extracellular edema, and that "treatment should be directed primarily toward hydrating the cells."

Some of our data can be fitted into McPhail's concept. Since sodium and chloride ions are confined almost wholly to extracellular water, restriction of salt intake might be expected to diminish somewhat the osmotic concentration of extracellular fluids. Adjustment is very quickly made to such concentration changes, and osmotic equilibrium between cells and extracellular water is maintained by two mechanisms: (1) a shift of water into the cells, and (2) diuresis. Forcing salt-free fluids in conjunction with salt restriction should accentuate both of these phenomena. The moderate salt restriction practiced by our pa-

Originally, only the destructive effects of irradiation were considered of therapeutic value in the control of dysfunctional uterine bleeding, inevitably resulting in temporary or permanent suppression of the menstrual function and in sterility. The use of nondestructive doses of roentgen rays for the purpose of relieving amenorrhea, the clinical antithesis of menometrorrhagia, was first tried during the second decade of this century.

Historical Sketch

A brief history of the development of low-dosage irradiation as a therapeutic agent is warranted. In 1910 and 1911 Cheron¹ and associates warned that x-ray exposures under 110 per cent skin erythema dose stimulate the growth of carcinoma of the uterus and increase the incidence of metastasis. Their deductions were later proved to be erroneous. However, these reports initiated an era of experimentation on the stimulating effects of irradiation on plants and lower animals. Hewer² induced sexual maturity in infantile rats with mild irradiation of the ovaries. This was probably due to irradiation of the anterior pituitary gland which, in small animals, is unintentionally but simultaneously exposed. Steinaeh and Kun³ induced hyperluteinization of the guinea pig's ovaries by x-ray treatment. Drips and Ford⁴ observed only slight congestion of the ovaries of rats that were killed shortly after the administration of a 10 per cent cutaneous erythema dose for the rat. The follicular apparatus was apparently not influenced by the procedure. Parkes⁵ observed ingrowth of epithelioid cords of cells from the periphery into the stroma of mouse ovaries that were intensively irradiated; the cords exhibited a tendency toward follicular arrangement. Epifanio and Cola⁶ observed a rapid increase in growth of young rabbits after low-dosage irradiation of the pituitary gland which at autopsy showed no evidence of cytologic alteration.

Clinically, Van de Velde⁷ reported in 1915 the return of normal ovarian function after small doses of x-rays had been applied over the ovaries. Soon thereafter similar results were reported by Hirsch,⁸ Rubin,⁹ Rongy,¹⁰ Kaplan,¹¹ and Drips and Ford.¹² Wagner and Schoenhof¹³ have found no degenerative changes in the ovaries of women subjected to low-dosage irradiation prior to panhysterectomy and bilateral salpingo-oophorectomy for carcinoma of the uterus. Only one of the ovaries of each patient was irradiated; the corresponding ovary was protected from the rays by means of proper screening for the purpose of histologic comparison.

More recently, a number of investigators also reported on the therapeutic value of low-dosage irradiation of the pituitary gland and ovaries in instances of amenorrhea with or without associated sterility (Table I). A composite review of these reports indicates a restoration of menstrual periodicity in 440 of 755 patients thus treated with no interference in the fertility in those who desired offspring.

Nevertheless, most clinicians regard it as a dangerous agent and are loath to employ it for fear of irreparable damage to the ovaries. This attitude toward low-dosage irradiation is mostly based upon animal experimentation with destructive doses.

The numerous clinical reports on low-dosage irradiation to the pituitary gland and ovaries cover only a short period of follow-up, one

The incidence of toxemia was not lowered in the patients who restricted both salt and fluids. This is partially attributable to a concentration of unfavorable cases in this group.

The incidence of toxemia was considerably lowered in the patients who restricted salt and forced fluids.

The effectiveness of prophylaxis against toxemia increased as greater weight losses were induced by the dietary regimes. Paradoxically, the gain or loss in extracellular water seemed to bear no relation to the incidence of toxemia; our data are inconclusive on this point.

We wish to acknowledge our indebtedness to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters for reading the typescript. The 2 gram salt diet was devised by Lorene Dickerson, chief dietitian at the Margaret Hague Maternity Hospital. The urinary creatinine determinations were done by Frances Orsato and Peter Marotta.

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LOW-DOSAGE IRRADIATION TO THE PITUITARY GLAND AND OVARIES IN AMENORRHEA AND DYSFUNCTIONAL UTERINE BLEEDING*

A Long-Term Survey

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DYSFUNCTIONAL menstrual disorders, with or without associated sterility, are the most difficult problems encountered by the gynecologist. The patients stop at nothing in their search for a cure. In most instances of dysfunctional menstrual disorders, especially amenorrhea of long duration, endocrine and other forms of therapy fail to produce consistent results.

Clinicians have long sought an agent capable of normalizing the menses and of relieving sterility of dysfunctional origin. It seems probable that this long-sought remedial agent has at last been discovered in the form of low-dosage irradiation.

*Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

NOTE: The cases herein reported were selected from the private practice of Dr. Charles Mazer.

deleterious effect upon the offspring of 54 women who have given birth to 80 children.

Illustrative of the harmlessness to the patient and to the progeny of the first generation, even of three courses of low-dosage irradiation to the pituitary gland and ovaries, is the following case record:

Mrs. M. S., aged 24 years, sought treatment in December, 1933, for the relief of amenorrhea of eight years' duration and inability to conceive for two years. Episodes of menometrorrhagia were frequent from the age of twelve to sixteen. Thereafter amenorrhea (three cycles per year) ensued for eight years. In the two years prior to low-dosage irradiation treatment, conception did not occur. In December, 1933, physical and general laboratory examination revealed nothing abnormal. Low-dosage irradiation, given in December, 1933, promptly normalized her menstrual cycles. She conceived in July, 1934, and delivered a normal full-term infant. She menstruated regularly until 1937 when the tendency to amenorrhea returned. In November, 1937, a second course of x-rays was given after a period of amenorrhea of eight months' duration. Partial improvement was obtained and a third course in March, 1938, regulated her menses to the date of this follow-up (May, 1942). During the interim she delivered two healthy infants.

This case record illustrates both the safety of even three courses of low-dosage irradiation to the ovaries of the patient and the harmlessness of the treatments upon the children of the first generation.

The hypothetical objection to low-dosage irradiation on the basis of its possible harmful effects upon the second and third generations cannot be relevantly argued since this remedial agent has been employed in this country less than two decades.

Modus Operandi of Low-Dosage Irradiation

Although twenty-seven years have elapsed since Van de Velde⁷ suggested low-dosage irradiation as a therapeutic agent, its modus operandi is still undetermined. Most radiologists maintain that roentgen rays rapidly produce hyperemia and that they are always destructive. For example, Thaler,¹⁴ Desjardins¹⁵ and others believe that the beneficial effects of low-dosage irradiation in the treatment of amenorrhea and dysfunctional uterine bleeding result from the destruction of a persistent corpus luteum or of an abnormally large Graafian follicle. They do not explain the phenomenal escape from damage of the remaining essential and more vulnerable elements of the ovaries.

Others, on the other hand, apply the term "stimulation therapy" to low-dosage irradiation because there is clinical evidence of functional stimulation of the irradiated glands without subsequent deleterious effects.

While the modus operandi of low-dosage irradiation remains controversial, the lasting restoration of menstrual periodicity in the majority of women who were thus treated as far back as 1927 points to a stimulative rather than to a destructive effect.

to three years. It is, therefore, of interest to learn what has happened to a representative group of these women and their offspring during a much longer follow-up period. A careful follow-up of 136 women who received low-dosage irradiation to the pituitary gland and ovaries from three to thirteen years ago forms the basis of this presentation. The results indicate that low-dosage irradiation, within the dosage limits employed in these cases, is a most helpful and safe agent in the armamentarium of the gynecologist. Moreover, the follow-up shows no

TABLE I. STATISTICS ON ROENTGEN RAY TREATMENT OF AMENORRHEA

Note: Improved cases grouped as failures

REPORTED BY	DURATION OF AMENORRHEA	AGE OF PATIENTS	GLAND IRRADIATED	NO. OF PATIENTS	NO. OF CURES FOR ONE OR MORE YEARS	NO. OF HEALTHY OFFSPRING	NO. OF ABORTIONS
Thaler ¹⁴	4 to 30 mo.	17 to 35 yr.	Ovary	62	40 (65%)	2	—
Werner ¹⁷	—	—	Pituitary	13	7 (54%)	—	—
Steinhardt ¹⁸	3 to 54 mo.	18 to 39 yr.	Pituitary	50	22 (44%)	2	—
Kaplan ¹⁹	1 mo. to 14 yr.	19 to 45 yr.	Pituitary and ovaries	117	79 (67%)	38	5
Drips ²⁰	—	29 single and 33 married women	Pituitary and ovaries	62	31 (50%)	11	—
Tamis ²¹	3 to 36 mo.	17 to 36 yr.	Pituitary and ovaries	25	15 (60%)	—	—
Edeiken ¹⁶	—	—	Pituitary and ovaries	56	40 (72%)	11	1
Rubin ⁹	—	19 to 33 yr.	Pituitary and ovaries	12	11 (93%)	8	1
Rongy ¹⁰	2 to 3 mo.	—	Pituitary and ovaries	13	5 (37%)	—	—
Porchownik ²²	—	16 to 39 yr.	Pituitary and ovaries	73	23 (31%)	20	6
Mazer and Goldstein ²³	3 to 36 mo.	20 to 35 yr.	Pituitary and ovaries	58	38 (66%)	20	5
Mazer and Spitz ²⁴	1 to 6 yr.	18 to 36 yr.	Pituitary and ovaries	74	41 (55%)	26	2
Mazer and Baer ²⁵	1 to 13 yr.	18 to 36 yr.	Pituitary and ovaries	106	62 (59%)	20	4
King ²⁶	$\frac{1}{2}$ to 3 yr.	—	Pituitary	10	10 (100%)	2	0
Bogart ²⁷	—	—	Pituitary and ovaries	24	16 (66%)	—	—

biologic test was performed to exclude a chance pregnancy, unless the patient happened to have had a menstrual flow within two weeks preceding the institution of treatment.

Effect on Secondary Amenorrhea

Fifty-one patients, ranging in age from 17 to 35 years, complained of infrequent menstruation for periods ranging from six months to fifteen years. Seven patients were totally amenorrheal for two or more years; 8 patients were totally amenorrheal for one year; and the remaining 36 patients menstruated at intervals of four or more months.

Thirty-six (71 per cent) were restored to normal menstrual periodicity during a follow-up period of three to thirteen years with an average of seven years for the group. Four of these patients conceived within three months after irradiation therapy. Three of the 4 reverted to their former state of amenorrhea after delivery but responded to a second course of treatment and have since been menstruating regularly even after subsequent deliveries. Five (9 per cent) were temporarily benefited and the remaining 10 (20 per cent) were unaffected by the irradiation.

The response to low-dosage irradiation seems to be inversely proportional to the duration of the disorder. For instance, only 3 (37 per cent) of the 8 women who were totally amenorrheal for one year or longer prior to therapy were cured, whereas 33 (76 per cent) of the remaining 43 patients who had had one to three menstrual periods during the year preceding treatment were cured.

Forty-six infants were born to 25 women of the amenorrheal group treated with low-dosage irradiation. Two of the 46 were stillborn from various causes; the remaining 44, now ranging in age from three to ten years, have developed mentally and physically to the predicted degree.

Effect on Primary Amenorrhea

Four patients, ranging in age from 18 to 22 years, had never menstruated. Their average age was 19.8 years and the follow-up period averaged 5.5 years. Three patients have remained amenorrheal, whereas the fourth began to menstruate spontaneously two years after treatment and continued to menstruate normally throughout a follow-up period of four years.

It is evident from a follow-up of this small number of patients that primary amenorrhea is not likely to respond to low-dosage irradiation of the pituitary gland and ovaries. A co-existing Müllerian tract defect may add to the difficulty in these cases.

Effect on Oligomenorrhea

Oligomenorrhea is a milder form of ovarian dysfunction than is frank amenorrhea and, therefore, yields more readily to therapy. Thirty-seven patients, ranging in age from eighteen to thirty-nine years, complained of oligomenorrhea for periods ranging from one to sixteen years. Their average age was twenty-six years, and they averaged 5.7 menstrual cycles per year.

Twenty-nine (78 per cent) were restored to normal menstrual rhythm during a follow-up period of three to nine years with an average of 5.2 years for the group; five (14 per cent) were temporarily benefited; 3 (8 per cent) remained unaffected by treatment.

Technique of Low-Dosage Irradiation

The patients herein reported were treated by several radiologists who employed the technique of Edeiken¹⁶ with uniformly good results. The treatment may be described as follows: One hundred and thirty-five kv., 5 ma. at a distance of 40 cm. with 6 mm. of aluminum filtration through an anterior pelvic field of 20 by 20 cm. Depending upon the thickness of the abdominal wall, 50 to 90 r., measured in air, are given three times at intervals of one week. The pituitary gland is treated with the same dosage at the same time through a portal of 3 by 3 cm. just above and posterior to the midpoint of an imaginary line joining the outer canthus of the eye and the external auditory meatus.

Partial relief of the amenorrhea by one course of treatment seemingly justifies a second course within three to six months. The harmlessness of a second course is demonstrated by 7 of 16 patients who received a second course of treatments within the dosage-level recommended. They conceived thirteen times, delivering 12 healthy offspring and one still-birth (cause unknown).

Of 249 patients thus treated by one gynecologist (C. M.) during the eleven-year period of 1927 to 1937, inclusive, 136 responded to a questionnaire submitted to them concerning menstrual periodicity, fertility, the number of offspring since treatment and the present physical and mental status of their children.

End-Results in One Hundred Thirty-Six Patients Treated With Low-Dosage Irradiation

The follow-up of 136 patients who received low-dosage irradiation to the pituitary gland and ovaries during the period of 1927 to 1937, inclusive, permits the following classification as to indications and results:

1. *Secondary amenorrhea*: Menstrual intervals of four or more months or years.
2. *Primary amenorrhea*: Embracing those patients who had never menstruated.
3. *Oligomenorrhea*: Menstrual intervals of six to thirteen weeks.
4. *Hypomenorrhea*: Regular menstruation with scanty flow.
5. *Menorrhagia*: Prolonged or excessive menstrual flow.
6. *Metrorrhagia*: Aeyelic uterine bleeding.

Selection of Patients for Low-Dosage Irradiation of the Pituitary Gland and Ovaries

Only those patients who after a careful history and physical examination showed no evidence of a constitutional debilitating disease, diabetes mellitus, or thyroid malfunction were subjected to this form of treatment. Nearly all of the patients had previously received organotherapy without improvement. In most of the patients with menometrorrhagia, a diagnostic curettage preceded low-dosage irradiation treatment to the pituitary gland and ovaries in order to eliminate the possible presence of intrauterine pathology. A careful pelvic examination eliminated uterine fibroids as the cause of bleeding. Women with premenopausal uterine bleeding were not treated with low-dosage irradiation. In almost all amenorrheal women subjected to low-dosage irradiation, a

Five (50 per cent) were restored to normal menstrual rhythm during a follow-up period of three to eleven years with an average of 7.2 years for the group; 3 (30 per cent) were temporarily benefited; and 2 (20 per cent) were unaffected by irradiation therapy. The history of one patient is unusually interesting and deserves recording:

Miss C. R., aged 25 years, sought relief from severe metrorrhagia in July, 1933, having stained or bled daily throughout the preceding eighteen months despite curettage and organotherapy. Examination revealed a moderately anemic but otherwise healthy patient. Low-dosage irradiation of the pituitary gland was administered in August, 1933, resulting in partial improvement during the following four months. In January, 1934, a second course of irradiation treatments was administered over the pituitary gland and ovaries, resulting in prompt establishment of normal menstrual rhythm which continued uninterrupted during the follow-up period of three and one-half years.

TABLE II. INDICATIONS FOR AND RESULTS OF LOW-DOSAGE IRRADIATION OF THE PITUITARY GLAND AND OVARIES

CONDITION	SECOND-ARY AMEN-ORRHEA	PRIMARY AMEN-ORRHEA	OLIGO-MENOR-RHEA	HYPO-MENOR-RHEA	MENOR-RHAGIA	METROR-RHAGIA	TOTALS
Number of patients	51	4	37	7	27	10	136
Average age of each group	25.9	19.8	26.0	24.8	27.1	26.8	—
Number of periods per year preceding treatment	2	never menstruated	5.7	11	—	—	—
Average duration of symptoms (years)	6.4	since puberty	6.8	6.7	2.0	1.2	—
Cures of 3 to 13 years	71%	0%	78%	57%	59%	50%	66%
Number of successful pregnancies	46	—	28	3	7	6	90
Number of abortions	—	—	3	1	—	3	7
Number of stillbirths	2	—	1	—	—	—	3

Summary and Conclusion

A long-term survey of the end-results of low-dosage irradiation of the pituitary gland and ovaries in amenorrhea and in dysfunctional uterine bleeding, with or without sterility, is presented.

Of 249 patients treated between 1927 and 1937, inclusive, 136 were followed up for periods ranging from three to thirteen years.

This method of treatment resulted in restoration of normal menstrual function in 71 per cent of 51 amenorrheal women; 78 per cent of 37 oligomenorrheal patients; 57 per cent of 7 hypomenorrheal women; 59 per cent of 27 menorrhagic women; and 50 per cent of 10 metrorrhagic women.

Of this group of 37 oligomenorrheal women, 23 complained of sterility. Following low-dosage irradiation of the pituitary gland and ovaries, 17 of these patients conceived and carried to term 23 healthy infants. Additionally, there were 5 pregnancies among those patients who did not complain of sterility. Of the 28 pregnancies, 24 were successfully carried to term; 3 terminated by abortion; and 1 terminated in a still-birth of unknown cause.

It is interesting to compare the results obtained with low-dosage irradiation in the three types of amenorrhea. The treatment totally failed in primary amenorrhea; it yielded 71 per cent permanent cure in secondary amenorrhea; and 78 per cent cure in oligomenorrhea.

Of the 92 patients in the three subgroups of amenorrhea, 65 (71 per cent) were restored to normal menstrual rhythm for a period of from three to thirteen years solely by the use of low-dosage irradiation therapy.

Effect on Hypomenorrhea

Hypomenorrhea, per se, is not disturbing to the patient until sterility, so frequently associated with it, becomes a major problem.

Of 7 hypomenorrheal women, 6 sought relief of associated sterility and only one complained of hypomenorrhea primarily. Their ages ranged from twenty to twenty-nine years and their symptoms were present for one to twelve years. Four (57 per cent) of the 7 patients were relieved during a period of four to nine years with an average of 6.3 years for the group; and 3 (43 per cent) remained unaffected by low-dosage irradiation. Only one patient was relieved of her sterility, resulting in two full-term healthy infants and in one abortion.

Effect on Menorrhagia

Twenty-seven patients, ranging in age from 14 to 43 years, menstruated cyclically but either excessively or for a prolonged interval. The duration of the menorrhagia was from three months to ten years.

Sixteen (59 per cent) were restored to normal menstrual rhythm by low-dosage irradiation during a follow-up period of three to eleven years with an average of 5.6 years for the group; 3 (11 per cent) were benefited temporarily; and the remaining 8 (30 per cent) were unaffected by treatment. Two patients, age 40 and 43, had normal cycles for three years after treatment before typical menopausal symptoms commenced. Two patients became temporarily amenorrheal for five and eight months, respectively, after irradiation and then normal rhythm was re-established. It is probable that both of these patients followed the usual clinical course of this type of dysfunction since menorrhagia is often a precursor to amenorrhea. Therefore these two patients are classified as therapeutic failures.

Of 4 menorrhagic patients complaining of sterility, only one was relieved. Seven pregnancies occurred in 5 of the group of 27 patients and all were successfully carried to term. All 7 children developed physically and mentally to their predicted degree.

Effect on Metrorrhagia

Ten patients, ranging in age from eighteen to thirty-six years, had totally acyclic menstrual rhythm for periods ranging from six months to four years, with an average of 1.2 years for the group. None complained of sterility.

THE USE OF HEROIN (DIACETYL-MORPHINE) IN LABOR*

A Report of 454 Deliveries

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AS FAR as can be determined there have been few, if any, clinical reports devoted exclusively to the study of diacetyl-morphine (heroin) in obstetrics. The primary aim of this study is to evaluate this drug as an obstetric analgesic agent. The end obtained may be historical as well as clinical unless modification is made of existing narcotic regulations which now prohibit the manufacture of heroin.

An ideal obstetric analgesic agent has been defined frequently as one which produces a maximum amount of pain relief with a minimum amount of danger to the mother and fetus. Certainly the evaluation of any method of obstetric analgesia must consider relief of pain as an essential property, yet the original definition fails to include many other properties, some of which are necessary and others are desirable. One essential characteristic is frequently overlooked in our search for an ideal obstetric analgesic agent: Is the drug adaptable to all environments with ease and safety? There are several methods of obstetric analgesia which produce excellent pain relief without significant hazards, yet they are highly specialized technical procedures with limited application. Another quality often wanted is the ability to give rest to a patient exhausted from a tiring labor. Some obstetricians, and patients as well, consider amnesia another indispensable characteristic. Equal consideration must be given the deleterious effect which analgesic drugs produce, and the harmful effects may be many and varied. Some of the important ones in obstetrics are death, asphyxia neonatorum, prolonged labor, increased incidence of operative deliveries, and injuries.

There are but two classes of nonvolatile agents in common use for relief of pain in labor, the analgesics and the hypnotics. Heroin, a synthetic opium derivative, is an analgesic agent and relieves pain without loss of memory and consciousness as do other opium derivatives. Barbituric acid derivatives, paraldehyde and scopolamine, are examples of hypnotic agents which produce sleep and amnesia; they relieve pain only when given in amounts sufficient to produce a loss of consciousness. Agents of both classes may be combined to produce analgesia and hypnosis.

Diacetyl-morphine was discovered and studied chemically by Wright¹ in 1874, it was also studied by Hesse² in 1884. In 1890 Dott and Stockman³ published an extensive account of morphine and its deriva-

*Aided by a grant from the Wisconsin Alumni Research Foundation.

Four patients with primary amenorrhea were unaffected by low-dosage irradiation therapy.

The percentage of cures for the group of 136 as a whole was 66. Two patients were temporarily made worse and the remaining 44 were either unaffected or only temporarily improved.

The restoration of menstrual function in 57 of the patients with associated sterility materially aided 34 of them in becoming pregnant.

Of the 90 pregnancies in 54 women of the group of 136, 80 resulted in full-term healthy offspring; 7 pregnancies terminated during the first trimester; and 3 terminated in stillbirths near term.

From this long-term follow-up it appears that preconceptual low-dosage irradiation to the pituitary gland and ovaries has no deleterious effect upon the generative organs or upon the offspring of the first generation.

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Seevers and Pfeiffer found that the peak of analgesic action for heroin was reached thirty minutes after subcutaneous administration while the peaks for dilaudid and morphine were reached in sixty and ninety minutes, respectively. The duration of heroin's analgesic action was shorter than that of morphine and dilaudid. There was little subjective depression following administration of heroin, but euphoria was great and furthermore, subjective depression was unassociated with analgesic properties. These investigators summarize their opinion of heroin as follows. . . "Heroin is unquestionably superior to the other drugs (morphine, dilaudid and ecodeine) from the subjective standpoint. On the other hand, these very qualities which accord it first place, likewise render it most dangerous from the standpoint of addiction, since its action is rapid and intense, side actions are few, and euphoria often supplants subjective depression. For the relief of acute attacks of pain, as in childbirth where a minimum of subjective depression is desired, this type of compound has a laudable action and its use would appear to be justified." However dangerous may be the tendency toward addiction it does not warrant serious obstetric consideration as a patient rarely receives more than one or two doses during the course of labor.

There has been little recognition of these singular properties of heroin by obstetricians. In his textbook, Davis¹² mentions that Williams, Webster, Bergland, Harris, and himself were among the few that had used heroin successfully in obstetric practice. Davis believes that heroin is vastly superior to morphine in its analgesic effect and furthermore he finds no decrease in intensity of uterine contractions. He also states that the drug has no deleterious effect on the child, an opinion we cannot confirm.

Methods and Materials

This study has been made upon private and ward patients of the State of Wisconsin General Hospital. The data were obtained after a careful study of the mother's record, the infant's record, and the anesthetist's record; the data then were placed on punch cards from which exhaustive compilations were possible. The total number of patients receiving heroin during labor was 454; of these, 362 were primigravidas and 92 were multigravidas. Our controls were obtained from the records of patients who were delivered during the same period of time but who had not received heroin or other nonvolatile analgesic agents. All patients received inhalation analgesia at the termination of labor. Obviously, superficial comparisons of the treated and untreated groups are hazardous, but we believe that comparable classes can be obtained by selection within the two groups.

There is no standard dose of diacetyl-morphine hydrochloride in obstetrics, the most common dose was gr. $\frac{1}{12}$, usually given as a single dose, occasionally as two doses of gr. $\frac{1}{24}$ each. A summary of the total dosage is as follows: 379 patients—gr. $\frac{1}{12}$, 51 patients—gr. $\frac{1}{6}$, 22 patients—gr. $\frac{1}{24}$, and 2 patients no data. Subcutaneous injection into the deltoid area was employed in every instance.

Results

From our observations it is possible to present data which illustrate some of the advantages and disadvantages of heroin according to the criteria set forth earlier in this report.

tives which included a description of diacetyl-morphine. No useful application of the drug was made until 1898 when the pharmacologic and chemical studies of Dreser⁴ introduced heroin* into general clinical practice,^{5, 6} not as an analgesic agent but as a substitute for codeine, particularly as a respiratory depressant. Harnack⁷ criticized Dreser for failing to give the proper scientific acknowledgement to the work of the earlier investigators. The first American report appeared in 1898 and in it Manges,⁸ following the dictates of Dreser, described the use of the drug as a respiratory depressant. The following year Manges⁹ reviewed the accumulated literature, by this time twenty-seven papers having appeared, and reported on his extended observations. At this time little mention was made of analgesic properties and nowhere was there reference to obstetric analgesia.

The name of the man who first administered heroin to parturient women is probably unknown and unrecorded. Because of the widespread use of heroin in medicine, the drug was probably used in obstetrics at an early date; if so, the record remains hidden. Some of us have often wondered why heroin was not widely received by obstetricians. Recall that at the turn of this century obstetric analgesia was limited to the second stage of labor except for an occasional administration of chloral or a comparable drug during the first stage of labor. The introduction of morphine-scopolamine narcosis by Steinbuckel in 1902 fixed the attention of the medical profession and the fancy of the public on painless labor. For fifteen years this method of analgesia remained popular but controversial, and the same fifteen years were the life span of heroin. By 1915 Congress had passed the Harrison act, forbidding the manufacture and importation of heroin, and thus it is credible that the use of heroin was completely eclipsed by the use of "twilight sleep" and consequently never received adequate obstetric trial.

Pharmacology

It is beyond the scope of this paper to detail the chemistry and pharmacology of diacetyl-morphine (heroin). This synthetic morphine derivative has the same general properties of morphine; both are narcotics, analgesics, respiratory depressants and are capable of producing addiction. Wright¹⁰ has recently presented evidence indicating that heroin is deacetylated quickly to morphine by certain enzymes of the tissues, notably of the liver. He believes that heroin may exert most of its pharmacologic activity as morphine. Heroin differs from morphine in the degree and duration of analgesia, in the intensity of subjective depression and euphoria and in the effect on the gastrointestinal tract. These differences have been long recognized by clinicians, most certainly by obstetricians, but not until recently have the accurate experimental data of SeEVERS and Pfeiffer¹¹ substantiated earlier opinion.

*Heroin was the trade name given to diacetyl-morphine by the Elberfelder Farbfabrik. The first American report by Manges spelled the word as heroin, however, the next American report, also by Manges, spelled the word heroine. This probably was the result of Anglicizing the German form heroin to heroine just as morphine and codeine became morphin and codein in German. Some American textbooks have continued to spell the word heroine. This is probably incorrect for the word heroin was a trade name and should not be changed in translation.

been described in detail in earlier reports.¹⁴ The essential points of difference are as follows: Mild asphyxia indicates spontaneous respiration delayed from one to five minutes, slight cyanosis and a conscious but sluggish infant. Many obstetricians would not consider such a baby abnormal. Moderate asphyxia indicates that the infant remains apneic from five to fifteen minutes but is readily resuscitated by artificial means, cyanosis is moderate. In severe asphyxia the infant is resuscitated with difficulty after fifteen or more minutes of apnea, there is marked cyanosis or pallor and the infant is unconscious and in shock.

TABLE II. ASPHYXIA NEONATORUM, COMPARISON OF HEROIN WITH MORPHINE AND CONTROLS

AGENT	NO. OF PATIENTS	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Heroin	447*	78.5	7.0	12.5	2.0
Morphine	72	69.0	12.5	12.5	6.0
Control	573	82.5	6.5	8.0	3.0

*Seven stillbirths excluded in calculation of asphyxia neonatorum.

Table II shows the incidence of neonatal asphyxia in three analogous groups of patients. The untreated or control group exhibited the least asphyxia neonatorum, the heroin group was next and the morphine group was greatest. Note also the type of asphyxia. The patients who received morphine had more mild and severe asphyxia neonatorum than did either of the other groups, but the incidence of moderate asphyxia was about the same whether heroin or morphine was given.

Heroin was not commonly used as an analgesic agent during premature labor; the number of administrations was limited to eight, nevertheless the incidence of asphyxia was high. Seven of the eight premature infants were asphyxiated at birth while a control group of 54 premature infants had 20 instances of asphyxia.

An attempt was made to correlate the incidence of asphyxia neonatorum with the amount of pain relief experienced by the mothers. The results obtained were inconclusive, however, there was slightly more asphyxia neonatorum when the mother had maximum pain relief. This point would bear further study by other investigators.

TABLE III. ASPHYXIA NEONATORUM IN RELATION TO TOTAL DOSAGE OF HEROIN

TOTAL DOSE	NUMBER	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Grains $\frac{1}{2}$ ₄	22	95.5	0	4.5	0
Grains $\frac{1}{12}$	379	79.5	7.5	11.0	2
Grains $\frac{1}{6}$ (in divided doses)	51	62.0	6.0	28.0	4
No data	2	(100.0)			

As might be expected, there was a direct correlation between the dosage of the drug and the incidence of neonatal asphyxia (Table III).

Most obstetricians agree that the timing of opiate administration is important if neonatal asphyxia is to be avoided and the usual concept is that morphine should be given at least four hours in advance of delivery. Knowing that heroin acts more quickly than other opiates we

Death.—There was but a single maternal death from the group of 454 women receiving heroin. This fatality was due to chronic lymphocytic leucemia and could in no way be attributed to analgesic medication.

Seventeen infants died; seven of these were stillbirths and ten were neonatal deaths. It was possible to divide the deaths into two groups; (Table I) those in whom death was unrelated to administration of

TABLE I. TOTAL MATERNAL AND INFANT MORTALITY LISTED ACCORDING TO CAUSE

CAUSE	NUMBER
Maternal Deaths	
Chronic lymphocytic leucemia	1
Total	1
Infant Mortality	
A. Those unrelated to heroin	
Congenital malformations	4
Prolapsed cord	2
Dystocia and trauma	3
Placenta previa, etc.	2
Total	11
B. Those related to heroin	
Premature infants under 3 pounds	4
Died during labor—cause ?	1
Apnea neonatorum	1
Total	6
Grand total, mothers	1
Grand total, infants	17

heroin (in this group death would have occurred whether or not analgesia had been given) and those in whom heroin may have been partially or wholly responsible. A word of explanation of the latter group is necessary for it included four premature infants. Although heroin was undoubtedly an element in the mortality of the premature infants, much of the responsibility rests with the obstetrician as there is little justification for the administration of any analgesic to a woman in premature labor unless specifically indicated by existing obstetric complications. The hazards of analgesics in premature labor have been demonstrated by Clifford,¹³ who found that administration of morphine to the mother resulted in a twofold increase in neonatal mortality, and by Lund¹⁴ who reported a signal increase in asphyxia neonatorum and neonatal death following the use of obstetric analgesic agents. The death resulting from apnea neonatorum must be charged directly to the heroin. Possibly the unaccountable death during labor should also be held to heroin, although this seems unlikely.

Asphyxia Neonatorum.—It is well to recall that obstetric analgesic agents may produce asphyxia neonatorum by direct means such as respiratory depression or production of cerebral edema, or by indirect means such as increasing the incidence of operative delivery or producing fetal anoxia.

It is also important to recognize the degree of neonatal asphyxia produced by any given drug. The classification used in this hospital has

produced mild asphyxia 13 times (3 per cent), moderate asphyxia 35 times (10.5 per cent). But no one can say how much the heroin was to blame.

Similar results were obtained from a study of a selected group of patients. The patients chosen for comparison were primigravidas without complications of pregnancy or labor, all were at term and all deliveries were spontaneous. Table VI compares the data from patients who received heroin with untreated patients. There was little "severe

TABLE VI. ASPHYXIA NEONATORUM AS OBSERVED IN PRIMIGRAVIDAS AT TERM HAVING UNCOMPLICATED SPONTANEOUS DELIVERIES WITH AND WITHOUT HEROIN

	NO. OF PATIENTS	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Heroin	124	84	6.5	9.5	0
Controls	212	90	5.5	4.0	0.5

asphyxia" in either group, both groups had about the same amount of "mild asphyxia" but there was a significant, though not alarming increase in "moderate asphyxia." The recorded increase in "moderate asphyxia" from 4.0 per cent to 9.5 per cent, in our opinion, may be attributed to the effect of heroin. From the results of these data, it would seem that heroin was responsible for about 3.5 to 5.5 per cent of asphyxia neonatorum.

Pain Relief.—It is most difficult to devise any satisfactory subjective or objective standards for the determination of pain relief in obstetrics, or for that matter, in clinical practice. Variations in the threshold of pain, in the psychic reaction to pain and in the reaction to analgesic drugs preclude any exacting measurement and leave us generalities only. Heroin produces little amnesia, thus the memory tests used by some obstetricians as an indicator of amnesia were of no value to us.

Two characteristic reactions have provided our basis for classification, one is analgesia and the other euphoria. We have previously mentioned that heroin is a powerful analgesic agent, and it produces few side actions such as psychic depression. Instead of depression it produces euphoria. This euphoria undoubtedly allays fear, and fear is closely linked with anticipation of pain. On the basis of such subjective criteria, the following results were obtained. The records of 290 of 454 patients (72 per cent) were sufficiently detailed to permit inclusion in this part of the study. Of these 290 patients, 56 per cent had good pain relief, 34.5 per cent had fair pain relief, and 9.5 per cent had poor or no pain relief.

Duration of Labor.—Labors over thirty hours in length were classified as prolonged and excluded from calculations for the following reasons. First, it is not our policy to use heroin as an analgesic agent in prolonged labor; morphine is the drug of choice. Second, many patients are referred to this hospital for delivery because of prolonged labor, and finally, in a study of only 454 patients, the frequency distribution of a few prolonged labors would seriously change the results. All of the prolonged labors were in primigravidas, 21 of 337 patients receiving heroin and 41 of 451 controls had prolonged labor.

The average duration of the first stage of labor in the control group of primigravidas was 11.8 hours, and in the group that received heroin it was 11.3 hours. Heroin was seldom given to multigravidas except when the first stage was longer or more severe than usual, hence the first

might expect the safe time interval of administration to be less than four hours. Table IV details the data observed. There is a surprising like-

TABLE IV. ASPHYXIA NEONATORUM IN RELATION TO INTERVAL BETWEEN ADMINISTRATION OF HEROIN AND DELIVERY

TIME INTERVAL	NO. OF PATIENTS	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Less than 1 hour	20	80	5.0	15.0	0
1-2 hr.	78	79	5.0	14.5	1.5
2-3 hr.	104	73	9.5	15.5	3.0
3-4 hr.	80	80	3.5	14.0	2.5
4-5 hr.	50	76	8.0	14.0	2.0
5-10 hr.	96	81	8.0	9.0	2.0
No data	19	89	5.5	5.5	0

ness of the results, particularly in the "moderate asphyxia" class where the values remain at about 15 per cent, the only exception is noted when delivery occurs from five to ten hours after administration of heroin. It is impossible to say how long an effective amount of heroin remains in the fetus. However, it is probably safe to assume that all effects of the drug have disappeared within ten hours. Clinical observation suggests that most of the maternal effects have vanished within five hours, and Table IV indicates that many or most of the fetal effects have likewise disappeared within five hours.

It is a well-established fact that many obstetric antecedents, such as dystocia, complications of pregnancy and labor, anoxia, operative delivery, and others contribute to the production of asphyxia neonatorum. These several factors may act alone or in combination with analgesic drugs. It is true also that the maternal need for sedation is greater when obstetrical difficulties are present. Each instance of asphyxia neonatorum was carefully reviewed after delivery and an attempt made to fix the etiologic responsibility. The results could be divided into three groups; those in which heroin was the sole factor, those in which obstetric factors such as trauma, anoxia and dystocia were accountable for the asphyxia, and those in which the heroin and obstetric factors shared the responsibility. Table V illustrates the results of 97 deliveries in which the infant was asphyxiated at birth.

TABLE V. CAUSES OF ASPHYXIA NEONATORUM AS OBSERVED IN THE 97 ASPHYXIATED INFANTS

CAUSE	NUMBER	PER CENT
A. Those related to heroin		
Heroin apparently sole cause	18	18.5
Heroin plus complicating obstetric factors such as dystocia, trauma bleeding, etc.	48	49.5
B. Those unrelated to heroin		
Obstetric complications sufficient to cause asphyxia regardless of the heroin, such as congenital malformations, anoxia, severe trauma and others	26	27.0
Unknown or unable to classify	5	5.0
Total	97 cases	

Further study of the 66 infants with asphyxia wholly or partly due to heroin reveals the following. Heroin was at fault 18 times, or 3.5 per cent, of the 447 deliveries. In combination with other factors heroin

reaction of the parturient woman to heroin is not euphoric in the sense just described, her reaction is rather a relief from tension and fear. This is especially true of the primigravida who is often extremely apprehensive about the anticipated difficulties of labor as well as the existing pain. In addition to the relief of corporal pain, heroin produces a tranquility of the mind which alone would likely justify the administration of the drug. This euphoria is undoubtedly disassociated from analgesia, frequently we have a diminution in the analgesic effects of heroin before delivery but rarely do we note a return of the initial apprehension and tension.

After administration of heroin the patients remain conscious and are capable of ordinary efforts of volition. They do not become excited, and there is no necessity for restraining devices or constant nursing attention. As a rule the patient dozes but does not sleep and there is no significant amnesia. The effects of heroin would undoubtedly seem ineffective to those obstetricians who desire amnesia, somnolence, and loss of consciousness for their patients. In fact, if these reactions are to be desired they cannot be obtained with heroin in dosages that are safe. If a drug is to be given for rest and sleep during prolonged labor, morphine rather than heroin would be the choice. If somnolence and amnesia are desired with the use of heroin they may be obtained by the addition of scopolamine although this addition may likely cause some increase in the incidence of asphyxia neonatorum.

The lack of subjective depression is of value in maintaining the cooperation of the patient, a fact of particular significance during the second stage of labor when bearing down efforts are attempted. Our results show that this cooperation is usually obtained as the incidence of operative delivery is only 3 per cent higher in the patients receiving heroin as compared with the controls.

It has always been our policy to give heroin at least three hours before the expected time of delivery. This has been done for two reasons; in the first place, we had a notion that there was a greater incidence of asphyxia neonatorum if the patient was delivered within the three-hour period; second, the combination of inhalation analgesia and heroin of recent administration frequently produced a sleepy and uncooperative patient during the second stage of labor. The data indicate that our prognostic ability was disappointing, for 201 of the 454 patients were delivered within three hours of administration of heroin; and of these 201 patients, about one-half were delivered in less than two hours. Most obstetricians believe that morphine when administered less than four hours before delivery increases the incidence of asphyxia neonatorum and, as we have said, this was our impression of heroin. The data have not substantiated this notion, for they indicate that the frequency of asphyxia neonatorum apparently is not related to the time interval between administration of the drug and delivery, the possible exception

stage of labor was 9.2 hours long when the mothers received heroin and 7.1 hours long in the control group. The duration of the second stage of labor was remarkably similar; primigravidas with heroin, 1 hour, 21 minutes; primigravidas without heroin, 1 hour, 18 minutes; multigravidas with heroin, 43 minutes; multigravidas without heroin, 43 minutes.

Operative Delivery.—There was no significant increase in the frequency of operative delivery in patients receiving heroin. Of 362 primigravidas receiving heroin, 48.5 per cent were delivered spontaneously, while spontaneous delivery occurred in 52 per cent of 484 primigravidas who did not receive heroin. Most of the operative deliveries were of the low forceps type. The incidence of breech delivery was about the same in both groups. Midforceps delivery was infrequent in the treated as well as the untreated patients, about $2\pm$ per cent, hence no comparison can be made.

Discussion

The data obtained from 454 deliveries permit an evaluation of heroin as an obstetric analgesic agent. This drug has certain notable properties, not exhibited by other opiates, which make it of particular value in obstetrics. Seevers and Pfeiffer¹¹ presented evidence which indicated that analgesia occurs independently of general narcosis and subjective depression in the normal human subject. Our clinical observations have led us to a similar conclusion in obstetrics.

Heroin differs from the other opiates by producing a high degree of analgesia in a short period of time. Because of this rapidity of action the drug should not be given with the onset of active labor as is common practice with some drugs, rather it should be given at a time when the patient has genuine discomfort. Ten or fifteen minutes after the subcutaneous injection of diacetyl-morphine hydrochloride gr. $\frac{1}{12}$ the patient will note the onset of analgesia, and within thirty minutes the analgesia will be at its peak. For about two hours there will be maximum relief from pain and then the effect gradually diminishes. As the analgesia disappears one of two courses may be considered, the heroin may be repeated or inhalation analgesic agents such as nitrous oxide-oxygen may be administered. If labor has not progressed according to expectation and delivery is not imminent, the heroin may be repeated, the dose varying from gr. $\frac{1}{24}$ to gr. $\frac{1}{12}$ according to the progress of labor. In our experience a second dose of the drug is not often necessary as the cervical dilatation is usually 8 cm. or more, and at this stage it is far more satisfactory to substitute gas analgesia. Heroin is not a satisfactory analgesic agent for the second stage of labor, although by acting as preanesthetic medication it may facilitate the administration of inhalation analgesia during the second stage of labor.

The lack of narcosis and subjective depression in the presence of analgesia places heroin apart from many analgesic agents. Instead of subjective depression there is euphoria. Euphoria is difficult to define but is commonly said to indicate a sense of well being or elation. The

heroin and various obstetrical complications. No one can say which of these two factors was more important, nevertheless, it is in this group that the incidence of asphyxia neonatorum may be reduced by careful evaluation of the mother and fetus before pain-relieving drugs are administered. In this respect heroin resembles other common obstetric analgesic agents.

Heroin was introduced as a substitute for codeine and it was soon advised as a therapeutic agent for every variety of chronic complaint including opiate addiction. Little wonder that the drug soon became disreputable. The preponderant criticism of heroin has unquestionably been the facility and frequency with which it produces addiction. Yet drug addiction is not a problem in the obstetric use of heroin for rather obvious reasons: The patients do not know what type of a drug they receive, the drug is rarely repeated more than once, and finally the drug is administered for temporary acute pain. Because of the minimal danger of addiction and because of the rather unique properties of heroin in obstetrics we are of the opinion that the manufacture of this drug should be permitted for purposes of pain relief in labor.

Summary and Conclusions

Diacetyl-morphine (heroin) is a synthetic opium derivative whose general characteristics are similar to those of morphine and dilaudid; all are analgesic agents, all are narcotics which produce addiction, all depress respiration and all have other common pharmacologic properties not pertinent to obstetrics. Heroin also differs from these opiates; it produces greater analgesia than morphine or dilaudid, it produces maximal analgesia within thirty minutes, it produces few annoying side reactions and it produces euphoria rather than psychic depression. Many of these qualities are of especial value in obstetrics. The predominant fault of heroin is its ability to produce addiction, yet this is distinctly of minor importance in obstetrics.

A clinical study of 454 patients who received heroin as an obstetric analgesic agent warrants the following conclusions:

1. Heroin produces a rapid and intense analgesia which persists from three to four hours and gives adequate analgesia in about 90 per cent of the patients.
2. Heroin produces a desirable psychic effect characterized by euphoria without depression or irritability of a physical or mental nature. This property is particularly valuable in allaying the apprehension and fear of some primigravidas.
3. There was no evidence of an increase in the duration of labor or an increase in the frequency of operative deliveries.
4. No adverse maternal effects were observed.
5. There were six infant deaths wholly or partially attributable to heroin, four of these occurred in small premature infants. Therefore heroin, as well as most other obstetric analgesic agents, is contraindicated in premature labor.

being an interval longer than five hours. The most plausible explanation seems to be that heroin is rapidly absorbed and the effects on the fetus are maximal within a short period of time after administration. We cannot designate that time interval, although it is probably less than an hour. A second and less likely explanation is that the several determinants of asphyxia neonatorum exert a greater influence than does heroin. In spite of these findings we do not advise indiscriminate use of heroin without some attention to timing. However, it is comforting to know that should our timing be inaccurate, and inaccurate it is, no additional hazards are created for the infant.

We hesitate to ascribe significance to any result based on the calculation of the duration of labor, for it is difficult of calculation and averages mean little even though the total number of patients is large. Some investigators are so indiscreet as to compare their average results, obtained by some specific treatment, to the average results of another investigator, the latter being considered a control. The results obtained by us should be reasonably significant when our treated and untreated patients are compared, but the data do not permit a comparison beyond this report. We observed no prolongation of labor following the use of heroin as an analgesic agent, neither did we observe any shortening of labor, although clinical observation at times led us to believe that occasionally labor progressed more rapidly after the drug was given.

We believe that heroin has many laudable and desirable features as an obstetric analgesic agent, and yet it is not the ideal drug for the purpose. In this respect heroin resembles every other obstetric analgesic agent for none is ideal and none can give maximum comfort without some sacrifice of safety for the mother and fetus. How great is that sacrifice of safety following the use of heroin?

There were no maternal deaths attributable to administration of heroin but the agent likely played a part in six fetal deaths. One of these fetal deaths was due to apnea neonatorum, undoubtedly the fault of heroin. Four premature infants died, and we believe heroin must be held as an adjuvant to these deaths. These deaths warrant a single conclusion, heroin is contraindicated in premature labor, as are all non-volatile analgesic agents.

In the study of asphyxia neonatorum we presented the results as observed in all deliveries and as observed in a selected series of deliveries. The first of these represents the amount of neonatal asphyxia which might be expected in routine clinical practice. The results observed in the selected series of cases give some indication of the neonatal asphyxia due to heroin alone. Both sets of results indicate that about $5\pm$ per cent of the infants were asphyxiated by heroin. This asphyxia is apparently unavoidable, it is not of the severe type and represents the price the infant must pay for maternal comfort. Approximately 10 per cent of the infants were asphyxiated by the combined effects of

THE RELATION OF CEREBRAL DYSRHYTHMIA TO ECLAMPSIA*

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IT MIGHT seem a bit strange that men oriented in the disciplines of neurology, psychiatry and neurosurgery should be concerned with such a foreign topic as the toxemias of pregnancy. It was our interest in the problem of the convulsive disorders that led to certain thoughts and speculations about the nature of convulsive phenomena associated with the toxemias of pregnancy.

The toxemias of pregnancy are usually classified as (A) pre-eclampsia (toxemia Grade I or Grade II in some clinics) and (B) eclampsia, the term eclampsia being reserved for those patients who develop convulsions or coma in the presence of the toxemia. Although the cause of these conditions is not known, most authorities believe that they are etiologically similar and therefore a single disease entity. However, why one patient develops convulsions as part of the syndrome and another remains free of convulsions is not clear. It is with this aspect of the problem of the toxemias that this paper will be concerned.

In recent years, with the aid of the electroencephalogram, a good deal of light has been shed on the problem of the convulsive disorders. In as much as my audience is probably not too familiar with certain of these new concepts, it might be pertinent at this point to review briefly some of the high spots of recent work in this field.

In 1929, Hans Berger of Jena² proved beyond doubt that the brain beats electrically. The instrument which he used to record the "brain waves" is called the electroencephalograph, and is very similar to the electrocardiograph. However, because the voltage obtained from the brain is only about $\frac{1}{100}$ of that produced by the heart, vacuum tube amplification was needed to obtain a satisfactory record. The technique of recording the tracings is quite simple. After small metal tags have been pasted to the scalp, the patient sits or lies quietly with his eyes closed for fifteen or twenty minutes while the electroencephalogram, familiarly called the electrocardiogram or "brain wave," is recorded. A "normal" record reveals "waves" with a frequency ranging from 8 to 12 per second, and although the voltage may vary considerably it is usually under 100 microvolts. This is sometimes referred to as the "alpha rhythm" (Fig. 1). The pattern of the record is modifiable by such activities as opening or closing the eyes, by sleep, pain or atten-

*Presented at a meeting of the Chicago Gynecological Society, October 16, 1942.

6. Heroin alone increased the incidence of asphyxia neonatorum by about 3 to 5 per cent, the increase was chiefly of the "moderate" type. The data suggest that heroin produces less asphyxia neonatorum than morphine.

7. The dosage should be kept minimal and should be given during the first stage of labor, preferably three or more hours before the anticipated time of delivery. There was no significant difference in the incidence of asphyxia neonatorum whether the infant was delivered one or five hours after administration of heroin.

Because of certain unique properties exhibited by heroin and not by other members of the opiate group and because of the minimal dangers of addiction when administered for the acute pain of parturition, we are of the opinion that the drug is of distinct value as an obstetric analgesic agent.

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example, of two patients with similar brain tumors, both as to type and location, one has convulsions and another does not. In accord with the above formulation, it would be suspected that the patient who developed convulsions associated with the brain tumor was predisposed by virtue of an associated cerebral dysrhythmia.

BRAIN POTENTIALS IN THREE TYPES OF SEIZURES

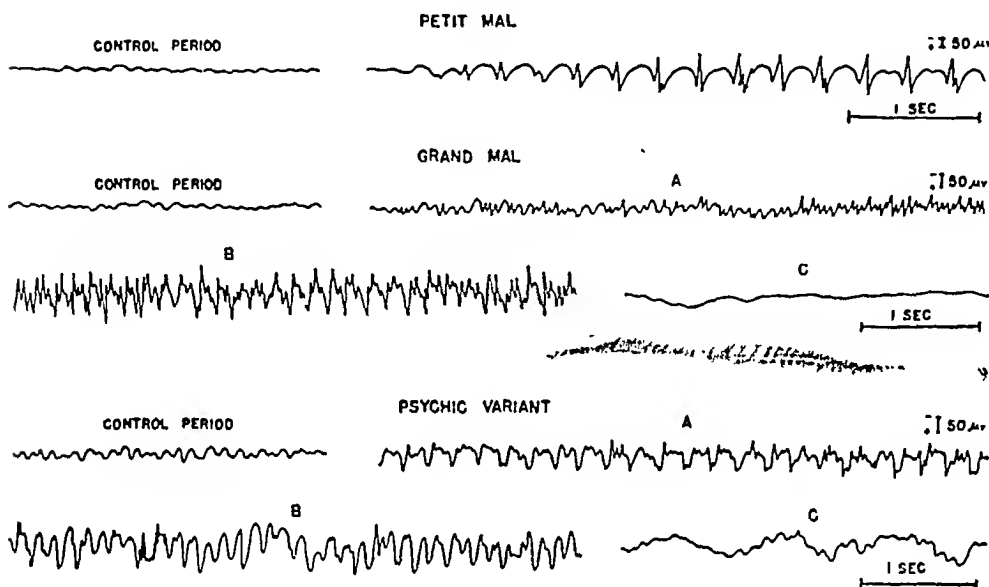


Fig. 2.—Examples of brain waves taken during attacks of petit mal, grand mal, and psychic equivalent. (From Gibbs, F. A., Gibbs, E. L., and Lennox, W. G.: *Brain* 15: 1937.)

PATIENT C.W. MANY PETIT MAL DAILY FAMILY HISTORY NORMAL

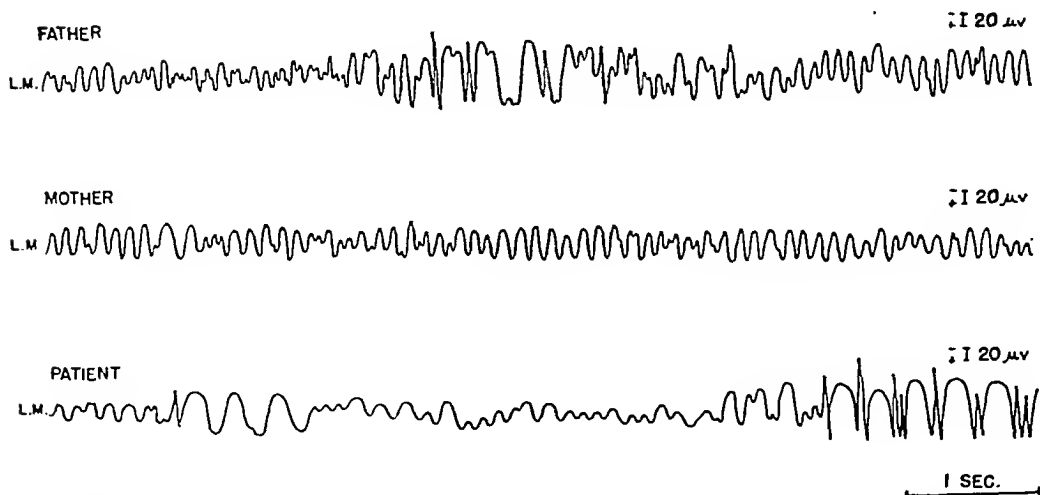


Fig. 3.—Record of abnormal cortical beat in the *clinically* normal father of an epileptic. Mother's record is borderline normal. (From same reference as Fig. 1.)

tion and other types of sensory and noxious stimuli. Under standard conditions a record is considered abnormal, if the waves are either too large (increased voltage, amplitude), too fast, or too slow (frequency).

Although practically all of the neurologic and psychiatric syndromes have been subjected to electroencephalographic study, the bulk of the work in this country has been devoted to the convulsive disorders. The pioneering studies of the Gibbs and Lennox of the Boston City Hospital revealed that there were "specific" abnormalities of the brain waves associated with epileptic attacks.³ These workers believe that the three classical types of epileptic attacks, namely grand mal, petit mal, and psychic (or psychomotor) equivalent, are associated with more or less characteristic types of abnormalities in the electroencephalogram *if the record is obtained during a clinical attack* (Fig. 2). But a much more important finding was that about 90 per cent of these patients had transient abnormalities of the brain waves when they were free from

EXAMPLES OF E.E.G.'S FROM CONTROL GROUP

NORMAL

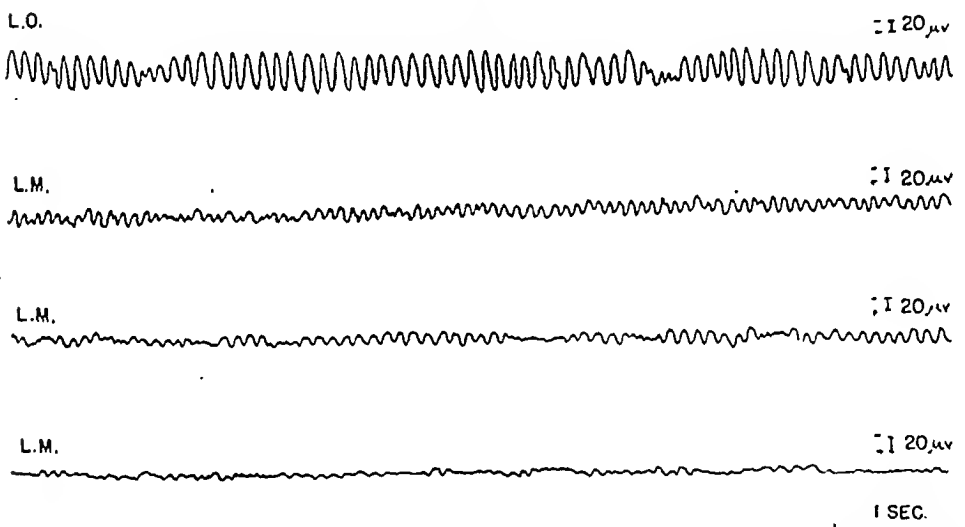


Fig. 1.—The electrical activity of the cortex of four normal subjects. (From Gibbs, F. A.: J. Pediat. 15: 749, 1939.)

objective or subjective evidence of seizures.⁴ In these free intervals the abnormalities may or may not be as specific as those recorded during a clinical seizure but they are definitely abnormal. Lennox has coined the term "cerebral dysrhythmia" to indicate such abnormalities.⁴ In the present state of our knowledge all we can say is that people who exhibit abnormal brain waves under so-called normal conditions are suffering from an inherent instability of the nervous system. In preliminary samplings, approximately 10 per cent of "normal" persons exhibit abnormalities similar to those seen in patients with seizures.⁴ These "asymptomatic dysrhythmia" individuals may, of course, go through life without developing convulsive phenomena. However, in the face of conditions which affect the central nervous system either by structural changes (brain tumors, trauma, syphilis, etc.) or by metabolic or physiopathologic changes (drugs, toxins, changes in blood chemistry, etc.) a predisposed person is more likely to develop convulsions. For